A guide towards safe, functional and renewable BPA alternatives by rational molecular design: structure–property and structure–toxicity relationships†

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Over the last few decades extensive research gave unambiguous evidence for the endocrine disrupting nature of bisphenol A (BPA), which has been an indispensable precursor in polymer chemistry since 1946. Unfortunately, current alternatives (e.g., bisphenol F and bisphenol S), are as endocrine active as BPA, emphasizing the need for a more multidisciplinary approach to design BPA alternatives, including a preliminary toxicity screening of the endocrine disrupting character in addition to performance screening. Moreover, the current topical transition towards a circular- and bio-economy stresses to adopt renewable resources to produce future chemicals and materials. To enable, inspire and stimulate the design of safer, functional and renewable BPA alternatives, this review gathered all research concerning bio-based bisphenol structures, their performance and *in vitro* oestrogenic activity. As a key structural feature providing high-performance polymer properties, only bio-based bisphenols with a diphenylmethane core scaffold, published in peer-reviewed papers, were included in this study. This focus revealed valuable structure–property and structure–toxicity relationships, providing the fundament for rational design of safe bisphenols.

1. Introduction

Bisphenol A (BPA) is a notorious but indispensable building block for the polymer industry. Its unique rigid molecular structure, characterised by a diphenylmethane (DPM) scaffold, provides good thermomechanical properties, chemical resistance and thermal stability to numerous polymers. In particular, it is the predominant precursor to synthesize high-performance polycarbonates and epoxy resins.^{1–3} Considering the impact of the COVID-19 pandemic, the global BPA market is estimated at 6.2 million metric tons in 2020 and expected to reach 7.1 million metric tons by 2027.⁴

Unfortunately, it has been shown that free monomeric BPA can leach out of consumer plastics (e.g., due to incomplete polymerization, (bio)chemical degradation and thermomechanical stress)^{5–7} contaminating the environment (e.g., surface

waters, soils, air)⁸ and resulting in human exposure.⁸ BPA has been detected in body fluids (e.g., human blood, urine) and tissues of children and adults.⁹ Over the last decades, extensive research associated multiple adverse health effects to human BPA exposure¹⁰ (e.g., cancer,^{11,12} reproductive issues,^{13,14} obesity¹⁵). In 2018, the European Chemicals Agency (ECHA) added BPA to the list of substances of very high concern (SVHCs), recognizing its endocrine disrupting activity and toxicity to reproduction.¹⁶ In addition, recent publications on the CLARITY-BPA study (*i.e.*, a collaboration between the US Food and Drug Administration (FDA) and academic scientists) showed effects of BPA on a variety of health-predictive or apical endpoints at the lowest dose tested of 2.5 µg per kg per day.¹⁷ Thereby highlighting the urgency to lower the current tolerated daily intake (TDI) by government agencies.¹⁸ This aspect, alongside the rising restrictions on BPA usage for certain applications (e.g., food packaging, baby bottles, thermal paper), emphasizes the need for safer BPA alternatives. BPA is currently being replaced by other, as endocrine active, bisphenols (*i.e.*, BPF, BPS),^{19,20} so-called ‘regrettable substitutions’.^{21,22}

Another challenge our society faces today is climate change. The current strategy endorsed by academic,²³ governmental²⁴ and industrial partners^{25,26} to lower the human footprint is

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the transition from a linear fossil-based economy to a circular bio-based economy. Herein, the use of renewable resources for sustainable, bio-based materials is key.^{23,27} Replacing BPA with not only a safer but also a renewable alternative that preserves its core structural feature (*i.e.*, DPM scaffold), would therefore lead to safer high-performance bio-based materials. In this regard, Liao *et al.* showed for instance that *via* the holistic bio-refining of sustainable wood, profitable, renewable and low carbon footprint chemicals can be attained.²⁸ More particularly, through the valorisation of lignin, the largest natural source of sustainable aromatics, *via* biorefinery processes (*e.g.*, reductive catalytic fractionation (RCF)) numerous phenolic monomers suitable for the synthesis of renewable bisphenols can be obtained.^{29–35}

Hence, the quest for safe, renewable and functional BPA alternatives is truly multidisciplinary in nature. As aptly stated by Paul T. Anastas: “The knowledge of the functional performance of a molecule is a minimal requirement. However, we must also understand the potential hazards of the molecule. Ideally, we would know what properties or structures dictate the functional performance and potential hazards.”³⁶ Accordingly, this review renders a systematic overview on bio-based bisphenols, their functional polymer performance (*i.e.*, characteristic polymer properties) and their potential hazards (*i.e.*, oestrogenic activity). Thereby, extracting valuable information on the structure–property and structure–toxicity relations to guide the rational design of non-regrettable BPA alternatives.

2. Bio-based monomers: bio-bisphenols

Fossil-based bisphenols are typically synthesized by reacting one mole of ketone/aldehyde with two moles of phenol in the presence a Brønsted acid catalyst. This condensation reaction consists of two consecutive electrophilic aromatic substitutions, *i.e.*, an hydroxyalkylation/alkylation reaction. In the latter water is released to form the hallmark bisphenol structure. This rigid molecular structure is characterised by a one-carbon bridge connecting two phenyl groups, the DPM core structure.^{1,2,37} The favoured alkylation position [*i.e.*, *ortho*- (*o*-) or *para*- (*p*-)] during the reaction determines the orientation of the carbon bridge to the hydroxyl groups, resulting in three different bisphenol regioisomers: the *p,p'*-, *o,p'*- and *o,o'*-isomer (Fig. S1, ESI†). In the synthesis of BPA-based polymers, only the *p,p'*-isomer is considered as a suitable building block for polymer chemistry. Hence, a high *p,p'*-bisphenol purity is required for the production of polycarbonates (>99%) and epoxy resins (>95%).^{2,38} It has been shown that the reactivity of the aldehyde influences the final isomer distribution. For instance, in the synthesis of bisphenol F (BPF) and BPA, where formaldehyde and acetone are used as carbonyl reagents respectively, the selectivity towards the *p,p'*-isomer is shown to be higher for BPA (88–95% *p,p'*, 5–13% *o,p'*- and negligible *o,o'*)³⁹ than for BPF (30–38% *p,p'*, 47–49% *o,p'* and 19–23%

o,o').^{40–42} Varying the carbonyl reagent not only influences the isomer distribution of the final bisphenol, but also gave rise to nowadays diverse bisphenol platform. In this review (synthetically pure) BPA, BPF and bisphenol E (BPE) were selected as reference bisphenols, characterised by a melting point (m.p.) of 158–159 °C, 162–164 °C and 123–127 °C, respectively (Table 1, Fig. 1 and 2).

Currently, the only bisphenol that is commercially available and (partially) bio-based, is *p,p'*-diphenolic acid, *p,p'*-DPA (5), which is produced on large scale from levulinic acid and phenol.^{43–45} Through esterification with different primary alcohols (*e.g.*, methanol, ethanol, ...), a series of *p,p'*-DPA esters is obtained (*i.e.*, DPA-Me (6), DPA-Et (7), DPA-*n*Pr (8), DPA-*n*Bu (9), DPA-*n*Pent (10)), their molecular structures are presented in Fig. 1. The ester series has a lower m.p. compared to that of *p,p'*-DPA (168–171 °C), decreasing with the alkyl chain length from 135 °C for *p,p'*-DPA-Me (6) to 100 °C for *p,p'*-DPA-*n*Pr (8) (Table 1, Fig. 2).^{46–49}

During the last decade, the substitution of reagents (*i.e.*, aldehyde, ketone and/or phenol) with bio-derivable alternatives gained research interest in the quest for a sustainable BPA alternative. This resulted in a plethora of new (partially) bio-based bisphenols (hereafter referred to as ‘bio-bisphenols’). All bio-bisphenols are summarized in Fig. 1 and in Table 1. To facilitate the comparison between compounds, a new nomenclature is introduced to associate the bio-bisphenol’s name with its molecular structure. Accordingly, the regioisomer orientation of the bisphenol (*e.g.*, *o,p'*, *p,p'*) is followed by three capital characters. The first two are related to the phenolic structures (*i.e.*, phenol (P), catechol (C), guaiacol (G) and syringol (S)). The character B, referring to ‘bis’, is used if the two phenol structures are the same. The third character refers to the carbon bridge of the bisphenols (*i.e.*, isopropylidene (A), methylenidene (F), ethylidene (E), *n*-propylidene (P)). The three capital characters might be followed by information about substituent(s) on the aromatic ring (*e.g.*, -4M, indicating a methyl substituent in position 4). An exception is made for well-known abbreviations, for instance, the commercial bio-bisphenol diphenolic acid and its derivatives (5–10).

Featuring the *p,p'*-isomer orientation, Harvey *et al.* (2016)⁵⁰ presented *p,p'*-BPF-3iP-6M (16), a bio-bisphenol synthesized by the acid-catalysed condensation of carvacrol and 1,3,5-trioxane. This bio-bisphenol was obtained as a white powder and it contains a DPM scaffold with alkyl substituents in position 3 and 6 relative to the hydroxyl group.⁵⁰ More recently, Yang *et al.* (2020)⁵¹ presented *p,p'*-BGF_{UR} (11), a DPM core structure with two *ortho* (*o*-) methoxy groups and a 2-furyl substituent on the carbon bridge, obtained by a base-catalysed coupling reaction of guaiacol and furfural. *p,p'*-BGF_{UR} was obtained as a white solid with 145 °C m.p.⁵¹ If catecholic reagents are used, a *p,p'*-orientated bio-bisphenol with four functional hydroxyl groups is acquired. This is shown by Jiang *et al.* (2018),⁵² using 4-methylcatechol and furfural or 5-hydroxymethylfurfural (HMF) in a base-catalysed condensation reaction *p,p'*-BCF_{UR}-3M (12) and *p,p'*-BCH_{MF}-3M (13), respectively, were obtained as solids.⁵²

Table 1 Physical appearance and m.p. of all (bio)-bisphenols included in this study. In addition, the general reaction mechanism, the reagents and catalyst in the bisphenol synthesis

Nr.	Name _{REF.}	Name _{NEW}	Reaction	Substrate 1	Substrate 2	Catalyst	Phase ^a	Colour	T _m [°C]	Ref.
Commercial petroleum-based <i>p,p'</i>-bisphenols										
—	<i>p,p'</i> -BPA	<i>p,p'</i> -BPA	Hydroxyalkylation/alkylation	Aceton	Phenol	Amberlyst-15	Solid	White	158–159	2
—	<i>p,p'</i> -BPE	<i>p,p'</i> -BPE	Hydroxyalkylation/alkylation	Acetaldehyde	Phenol	Brønsted acid catalyst	Solid	White	123–127	1
—	<i>p,p'</i> -BPF	<i>p,p'</i> -BPF	Hydroxyalkylation/alkylation	Formaldehyde	Phenol	Brønsted acid (zeolite) catalyst	Solid	White	162–164	42
Commercial bio-based <i>p,p'</i>-bisphenols										
5	<i>p,p'</i> -DPA	<i>p,p'</i> -DPA	Hydroxyalkylation/alkylation	Levulinic	Phenol	Brønsted acid catalyst	Solid	White	168–171	44
Bio-based <i>p,p'</i>-bisphenols										
1	<i>p,p'</i> -BGP	<i>p,p'</i> -GPF	Hydroxyalkylation	<i>p</i> -Vanillyl alcohol	Phenol	Amberlyst-15	Solid	—	122	60
2	<i>p,p'</i> -BGF	<i>p,p'</i> -BGF	Hydroxyalkylation	<i>p</i> -Vanillyl alcohol	Guaiacol	Dowex DR-2030	Solid	White	102–105	58
2	<i>p,p'</i> -BGF	<i>p,p'</i> -BGF	Hydroxyalkylation	<i>p</i> -Vanillyl alcohol	Guaiacol	Amberlyst-15	Solid	White	100–106	59
3	<i>p,p'</i> -BGS	<i>p,p'</i> -GSF	Hydroxyalkylation	<i>p</i> -Syringyl alcohol	Guaiacol	Amberlyst-15	Solid	—	95	60
4	<i>p,p'</i> -BGM	<i>p,p'</i> -BSF	Hydroxyalkylation	<i>p</i> -Syringyl alcohol	Syringol	Amberlyst-15	Solid	—	104	60
6	MePA	<i>p,p'</i> -DPA-Me	Esterification	<i>p,p'</i> -DPA	Methanol	<i>p</i> -Toluenesulfonic acid	Solid	—	133–134	46
6	MPA	<i>p,p'</i> -DPA-Me	Esterification	<i>p,p'</i> -DPA	Methanol	<i>p</i> -Toluenesulfonic acid	Solid	—	—	47
6	MDP	<i>p,p'</i> -DPA-Me	Esterification	<i>p,p'</i> -DPA	Methanol	Sulfuric acid	Solid	White	135	48
6	MPA	<i>p,p'</i> -DPA-Me	Esterification	<i>p,p'</i> -DPA	Methanol	<i>p</i> -Toluenesulfonic acid	Solid	White	133–134	49
7	EDP	<i>p,p'</i> -DPA-Et	Esterification	<i>p,p'</i> -DPA	Ethanol	sulfuric acid	Solid	White	130	48
7	EDPA	<i>p,p'</i> -DPA-Et	Esterification	<i>p,p'</i> -DPA	Ethanol	HCl	Solid	—	129	46
8	n-PrDPA	<i>p,p'</i> -DPA-nPr	Esterification	<i>p,p'</i> -DPA	<i>n</i> -Propylalcohol	HCl	Solid	—	100–101	46
9	BDP	<i>p,p'</i> -DPA-nBu	Esterification	<i>p,p'</i> -DPA	1-Butanol	H ₂ SO ₄	Solid	Light yellow	48	
10	PDP	<i>p,p'</i> -DPA-nPent	Esterification	<i>p,p'</i> -DPA	1-Pentanol	H ₂ SO ₄	Solid	Light yellow	48	
11	FBP	<i>p,p'</i> -BGF _{UR}	Hydroxyalkylation/alkylation	Guaiacol	Furfural	NaOH	Solid	White	145	51
12	MF	<i>p,p'</i> -BCF _{UR} -3M	Hydroxyalkylation/alkylation	4-Methylcatechol	Furfural	NaOH	Solid	—	—	52
13	MH	<i>p,p'</i> -BCH _{MF} -3M	Hydroxyalkylation/alkylation	4-Methylcatechol	HMF	NaOH	Solid	—	—	52
14	DHEO-dimer	<i>p,p'</i> -BCF-3P	<i>o</i> -Demethylation	<i>m,m'</i> -BGF-4P	—	48% HBr	Liquid	—	—	57
15	VAMC	<i>p,p'</i> -GCF-3M	Hydroxyalkylation	<i>p</i> -Vanillyl alcohol	4-Methylcatechol	H ₂ SO ₄	Solid	Orange	—	61
16	Carv	<i>p,p'</i> -BPF-3IP-6M	Hydroxyalkylation/alkylation	Carvacrol	1,3,5-Trioxane	HCl	Solid	White	—	50
17	IUPAC	<i>p,p'</i> -BPF-3M	Deoxygenation	<i>m,m'</i> -BGF-4M	—	—	Solid	White	—	56
18	IUPAC	<i>p,p'</i> -BPE-3M	Deoxygenation	<i>m,m'</i> -BGE-4M	—	—	Solid	White	—	56
19	IUPAC	<i>p,p'</i> -BPP-3M	Deoxygenation	<i>m,m'</i> -BGP-4M	—	—	Solid	White	—	56
Bio-based <i>o,p'</i>- and <i>m,p'</i>-bisphenols										
20	<i>o,p'</i> -BGP	<i>o,p'</i> -GPF	Hydroxyalkylation	<i>p</i> -Vanillyl alcohol	Phenol	Amberlyst-15	Solid	—	108	60
21	<i>o,p'</i> -BGF	<i>o,p'</i> -BGF	Hydroxyalkylation	<i>o</i> -Vanillyl alcohol	Guaiacol	Amberlyst-15	Solid	White	104	59
22	<i>m,p'</i> -BGF	<i>m,p'</i> -BGF	Hydroxyalkylation	<i>m</i> -Vanillyl alcohol	Guaiacol	Amberlyst-15	Solid	White	120	59
23	<i>m,p'</i> -BGS	<i>m,p'</i> -GSF	Hydroxyalkylation	<i>p</i> -Syringyl alcohol	Syringol	Amberlyst-15	Solid	—	81	60
24	<i>m,p'</i> -BGM	<i>m,p'</i> -BSF	Hydroxyalkylation	<i>p</i> -Syringyl alcohol	Syringol	Amberlyst-15	Solid	—	119	60
Bio-based <i>o,o'</i>- and <i>m,m'</i>-bisphenols										
25	IUPAC	<i>o,o'</i> -BGF-4M	Hydroxyalkylation/alkylation	Creosol	Formaldehyde	Zn(AC) ₂ ·2H ₂ O	Solid	—	123–125	53
26	IUPAC	<i>m,m'</i> -BGF-4M	Hydroxyalkylation/alkylation	Creosol	Formaldehyde	2.5 M HCl	Solid	—	131–134	53
26	<i>m,m'</i> -BGF-4M	<i>m,m'</i> -BGF-4M	Hydroxyalkylation/alkylation	Creosol	Formaldehyde	2.5 M HCl	Solid	White	138	54
26	IUPAC	<i>m,m'</i> -BGF-4M	Hydroxyalkylation/alkylation	Creosol	Formaldehyde	Lignosulfonic acid (LSA)	Solid	—	134–136	73
27	IUPAC	<i>m,m'</i> -BGE-4M	Hydroxyalkylation/alkylation	Creosol	Acetaldehyde	2.5 M HCl	Solid	—	143–146	53
28	IUPAC	<i>m,m'</i> -BGP-4M	Hydroxyalkylation/alkylation	Creosol	Propionaldehyde	6 M HBr	Liquid	—	—	53
29	<i>m,m'</i> -BGF-4E	<i>m,m'</i> -BGF-4E	Hydroxyalkylation/alkylation	4-Ethylguaiacol	Formaldehyde	2.5 M HCl	Solid	Yellowish	129	54
30	<i>m,m'</i> -BGF-4P	<i>m,m'</i> -BGF-4P	Hydroxyalkylation/alkylation	4-Propylguaiacol	Formaldehyde	2.5 M HCl	Solid	Yellowish	78	54
30	DHE-dimer	<i>m,m'</i> -BGF-4P	Hydroxyalkylation/alkylation	4-Propylguaiacol	Formaldehyde	48% HBr	Liquid	—	—	57
31	<i>m,m'</i> -BSF-4M	<i>m,m'</i> -BSF-4M	Hydroxyalkylation/alkylation	4-Methylsyringol	Formaldehyde	2.5 M HCl	Solid	Low-coloured	144	55
32	<i>m,m'</i> -BSF-4P	<i>m,m'</i> -BSF-4P	Hydroxyalkylation/alkylation	4-Propylsyringol	Formaldehyde	2.5 M HCl	Solid	Low-coloured	103	55

^a Phase at room temperature (RT).

Fig. 1 Overview of all (bio-)bisphenols included in this study. Representation of reported (bio-)bisphenols, their molecular structure and corresponding abbreviation according to the suggested nomenclature (*vide infra*).

If *para*-alkylated phenols are used in the aromatic substitution reaction, alkylation in *ortho*- and *meta*-position is observed. In Brønsted acidic conditions, the *meta*-alkylation is favoured by the presence of mesomeric and inductive electron-donating groups (*e.g.*, hydroxyl, methoxy) in *ortho*-position to the hydroxyl group. Given that bio-derived phenolic com-

pounds are often characterised by the presence of *p*-alkyl groups (*e.g.*, 4-*n*-propyl), *o*-methoxy groups (*e.g.*, guaiacol, syringol) and *o*-hydroxyls (*e.g.*, catechol, pyrogallol), this *meta*-alkylation (relative to the hydroxyl group) is a unique feature of bio-based substrates in aromatic substitution reactions.

Fig. 2 Melting point [°C] of all (bio-)bisphenols included in this study.

In this regard, Meylemans *et al.* (2012)⁵³ synthesized *m,m'*- and *o,o'*-bio-bisphenols by coupling 4-methylguaiacol (*i.e.*, creosol) with different aldehydes (*i.e.*, formaldehyde, acetaldehyde and propionaldehyde). Using a Brønsted acid catalyst, a high selectivity towards the *m,m'*-isomer was obtained (*i.e.*, >96% *m,m'*; <4% *o,m'*), resulting in *m,m'*-BGF-4M (26), *m,m'*-BGE-4M (27) and *m,m'*-BGP-4M (28). The use of a Lewis acid catalyst ($\text{Zn}(\text{Ac})_2 \cdot 2\text{H}_2\text{O}$) favoured the alkylation in *ortho*-position, yielding *o,o'*-BGF-4M (25). The *o,o'*-isomer of BGF-4M showed a lower m.p. than the *m,m'*-isomer, being 123–125 °C and 131–134 °C, respectively. A higher m.p. (143–146 °C) was observed for *m,m'*-BGE-4M (27), showing that a methyl substituent on the carbon bridge increases the melting point. In contrast, this trend is not shown by the bisphenol references BPF and BPE, where a methyl substituent on the carbon bridge lowers the melting point. However, further elongation of the bridging alkyl chain lowered the m.p. significantly, as *m,m'*-BGP-4M (28) was obtained as a viscous oil.

Koelewijn *et al.* (2017),⁵⁴ (2018)⁵⁵ extended the *m,m'*-bisphenol platform by coupling lignin-derived 4-*n*-propylguaiacol and 4-*n*-propylsyringol with formaldehyde under acidic conditions. Furthermore, the phenolic compounds 4-methylguaiacol, 4-ethylguaiacol and 4-methylsyringol were used to obtain a series of structurally related bio-bisphenols: *m,m'*-BGF-4M (26), *m,m'*-BGF-4E (29), *m,m'*-BGF-4P (30), *m,m'*-BSF-4M (31) and *m,m'*-BSF-4P (32). Looking into the melting point and thermal stability of these bio-bisphenols, Koelewijn *et al.* showed that (i) elongation of the 4-alkyl chain decreases the melting point, m.p. 138 °C > 129 °C > 78 °C (for 4-Me, -Et, -*n*Pr *m,m'*-bisguaiacols) and 144 °C > 103 °C (for 4-Me and -*n*Pr *m,m'*-bissyringols) (Fig. 2), (ii) the presence of an additional *o*-methoxy group increases the melting point with about 25 °C and (iii) the bio-bisphenols show similar, or even higher for *m,m'*-BGF-4P (30), thermal stability compared to BPA. Note that the combination of a lower melting point and similar thermal stability (*cf.* BPA) results in a broader liquid-state processing window of these bisphenols.^{54,55}

As a key characteristic of BPA, the *p,p'*-isomer orientation is still preferred in the design of a sustainable BPA alternative. Harvey *et al.* (2015)⁵⁶ converted *m,m'*-BGF-4M (26), *m,m'*-BGE-4M (27) and *m,m'*-BGP-4M (28) to *p,p'*-isomers by deoxygenation and hydrolysis, resulting in *p,p'*-BPF-3M (17), *p,p'*-

BPE-3M (18) and *p,p'*-BPP-3M (19).⁵⁶ Another conversion of a *m,m'*-isomer is presented by Zhao *et al.* (2016),⁵⁷ through an *o*-demethylation of *m,m'*-BGF-4P (30), *p,p'*-BCF-3P (14), a compound containing four hydroxyl groups, was obtained.⁵⁷

A more (carbon-)efficient way to synthesize *p,p'*-bio-bisphenols was presented by Hernandez *et al.* (2016).⁵⁸ Through the use of a phenolic compound featuring an intrinsic reactivity towards alkylation in *para*-position (*i.e.*, *p*-vanillyl alcohol), a 'short-cut' reaction mechanism with only one alkylation step is attained, resulting in a higher selectivity towards the *p,p'*-isomer. When *p*-vanillyl alcohol was coupled with guaiacol in the presence of a heterogeneous ion-exchanging catalyst (*i.e.*, Amberlyst-15), only three different regioisomers of BGF were obtained: the *p,p'*-(2), *m,p'*-(22) and *o,p'*-isomer (21), with an isomer distribution of 82%, 15% and 3%, respectively. To investigate the physical appearance and properties of the *m,p'*- and *o,p'*-isomer, Koelewijn *et al.* (2019)⁵⁹ selectively synthesized these isomers using vanillyl alcohol isomers (*e.g.*, *m*- and *o*-vanillyl alcohol), thereby shifting the isomer distribution. Interestingly, the *m,p'*-isomer showed a significantly higher melting point (119–120 °C) than the *p,p'*- (99–100 °C) and *o,p'*-isomer (103–105 °C).

Nicastro *et al.* (2018)⁶⁰ extended the substrate scope for this short-cut reaction using other phenolic compounds, like phenol and syringol. Because of the substrates varying amount of *o*-methoxy group(s), bisphenols with different isomer orientations and distributions were obtained. For example, coupling of *p*-vanillyl alcohol with phenol yielded 81% of *p,p'*-GPF (1) and 19% *o,p'*-GPF (20), whereas coupling with syringol gave 79% of *m,p'*-GSF (23) 21% of *p,p'*-GSF (3). Hence, the presence of a second *o*-methoxy group in syringol, compared to guaiacol, promoted the alkylation in *meta* to the hydroxyl group. In addition, *p*-syringyl alcohol was coupled with syringol to obtain 76% of *m,p'*-BSF (24) and 24% of *p,p'*-BSF (4). After isolation, the melting points of all bio-bisphenols were determined. Despite a variation in m.p. ranging from 81 °C to 122 °C, there is no clear correlation between the melting point and isomer orientation or amount of *o*-methoxy groups of the bio-bisphenols.⁶⁰

In 2019, Zhao *et al.*⁶¹ reported the synthesis of a bio-bisphenol characterised by three hydroxyl groups. Coupling *p*-vanillyl alcohol with 4-methylcatechol in the presence of an acid catalyst, *p,p'*-GCF-3M (15) was obtained as an orange solid.⁶¹

The current bio-bisphenol platform counts, to the best of our knowledge, 32 bio-bisphenols, from which 22 were directly derived from phenolic lignin monomers (e.g., 4-methylcatechol, guaiacol, syringol) and 4 were indirectly obtained from some of the previous ones (e.g., deoxygenation, demethylation). The use of lignin-derived phenols brought out new bisphenol isomer orientations (i.e., m,p' and m,m') in addition to the conventional isomer orientations (i.e., o,o' , o,p' and p,p'). Moreover, sugar-derived aldehydes and ketones (e.g., furfural, HMF, levulinic acid) proved to be efficient coupling agents, introducing interesting functional groups on the bisphenol carbon bridge. Except for p,p' -BCF-3P (**14**) and m,m' -BGP-4M (**28**), all bio-bisphenols were obtained as solids with m.p. ranging from 78 °C for m,m' -BGF-4P (**30**) to 171 °C for p,p' -DPA (**5**) and colours varying from white to light yellow and orange.

3 Bio-based polymers: structure–property

As previously mentioned, BPA is used for the synthesis of numerous polymers, including thermoplastic (e.g., polycarbonates, polyesters) and thermosetting (e.g., epoxy resins, cyanate ester resins and benzoxazine resins) polymers. The polycarbonate and epoxy resins industry are the main sales markets for BPA, demanding 66% and 30% of the global production capacity, respectively.² In addition, BPA is an important precursor for more specialized high-performance thermosets, like cyanate ester and benzoxazine resins. Depending on the author's interest, different polymers were synthesized from the presented bio-bisphenols (Fig. 1), an underlined number (e.g., (**1**)) is used to refer to the polymer or resin from the corresponding bio-bisphenol (e.g., (**1**)). Hence, the following section is subdivided in five polymer sections: polycarbonates, polyesters, epoxy resins, cyanate ester resins and benzoxazine resins, to reveal valuable structure–property relations.

The two polymer properties, that are discussed for all polymers, are (i) the thermal stability and (ii) the glass transition temperature (T_g). In general, thermogravimetric analysis (TGA) is used to assess the polymer's thermal stability. Unless stated otherwise, the experiment was performed under a nitrogen atmosphere. The thermal stability is defined by several parameters being (i) the onset degradation temperature ($T_{d5\%}$), (ii) the 10% weight loss temperature ($T_{d10\%}$), (iii) the 50% weight loss temperature ($T_{d50\%}$), (iv) the maximal degradation temperature (T_{max}), and (v) the char yield at a specified temperature (e.g., 600 °C, 800 °C). In what follows, mostly, $T_{d5\%}$ and T_{max} will be used to discuss the polymer thermal stability, if T_{max} is not given, $T_{d50\%}$ is given instead. The glass transition temperature (T_g) is determined using differential scanning calorimetry (DSC) for the thermoplastic polymers, and through dynamic mechanical analysis (DMA) for the thermosetting polymers. Although different parameters are used in literature to define T_g in a DMA experiment, the T_g reported in the following is, unless stated otherwise, the temperature where $\tan(\delta)$ reaches a maximum (i.e., $\max \tan(\delta)$).

In addition to the general thermomechanical properties, more specific polymer properties characterising each polymer type will be introduced and discussed, including for the thermoplastic polymers: the amorphous/crystalline phase and the solubility, and for the thermosetting polymers: the melting point of the uncured resins, the cure kinetics, processing window and more specifically water uptake and the LOI index (i.e., an index parameter of the flame resistance, that should be higher than 26⁶²).

3.1 Polycarbonates

Since 1957, an interfacial polymerization reaction of BPA and phosgene (i.e., the phosgene process)⁶³ is used to produce polycarbonates (PCs) on a large scale (Fig. S2a, ESI†).⁴⁶ Today BPA is still the leading precursor for the polycarbonate (PC) synthesis. The rigid molecular structure of BPA provides a PC with unique physical and chemical properties.^{64,65} BPA-Polycarbonate (BPA-PC) is a resilient polymer from which objects with high toughness and impact strength can be manufactured. Induced by its amorphous nature, BPA-PC shows excellent transparency, making it suitable for glass applications. Furthermore, BPA-PC is characterised by a high glass transition temperature (T_g) of 145 °C abiding high process temperatures, for instance, steam sterilization. However, it has been reported that long-term effects of hot water and steam might cause stress cracks and BPA leachates.^{66–68} Lastly, commercial BPA-PC show a high thermal stability, with $T_{d5\%}$ above 445 °C, a T_{max} and $T_{d50\%}$ above 500 °C and char yield >25% at 600 °C. This indicates an intrinsic flame retardant behaviour, through its ability to form polyaromatic char.^{64,65}

The development of a bio-based BPA-PC alternative reaching the same excellent polymer properties is challenging. To evaluate the performance of today's bio-bisphenol alternatives in PCs, three characteristic properties were selected: (i) the amorphous nature (i.e. inducing optical transparency⁶⁹), (ii) the glass transition temperature (T_g) and (iii) the thermal stability. Noteworthy, it has been shown that the mass-average molecular weight ($\bar{M}_w$) and dispersity ($\mathcal{D}$) influence T_g and thermal stability of PCs. In general, a higher $\bar{M}_w$ (same $\mathcal{D}$), results in a higher T_g ⁷⁰ and thermal stability.⁷¹ Hence, parameters such as $\bar{M}_w$ and $\mathcal{D}$ should be considered when comparing the different polymer properties. The bio-bisphenols used in PC chemistry and their mutual structural relations are shown in Fig. 3. All collected data concerning the PCs and their polymer properties are summarized in Table 2 and Fig. 4.

In 2019, Koelewijn *et al.*⁵⁹ determined the influence of the lignin-characterising *o*-methoxy groups on the PC synthesis and final polymer properties, comparing the PCs synthesized from p,p' -BGF (**2**) and p,p' -BPF.⁵⁹ A first observation concerns the solubility of the monomers and their corresponding PCs. Compared to p,p' -BPF, p,p' -BGF (**2**) was found to be more soluble in dichloromethane (DCM), the solvent of choice for the interfacial polymerization reaction of PC, resulting in a higher polymer yield for the bio-based PC. In contrast to the *quasi*-insoluble p,p' -BPF-PC, the final p,p' -BGF-PC (**2**) was found moderately soluble in DCM. The presence of the

Fig. 3 Bio-bisphenols used for the synthesis of polycarbonates. The representation of all so far reported bio-bisphenols, in addition to the petroleum-based references, used for the synthesis of (partially) bio-based polycarbonates and their structural relations.

o-methoxy groups lowered T_g of the PCs by 8 °C, from 114 °C for *p,p'*-BPF-PC to 106 °C for *p,p'*-BGF-PC (**2**). The authors attributed this decrease in T_g to the loss of segmental symmetry in the mono-substituted phenyl ring (*i.e.*, guaiacol), resulting in a less efficient packing, thus, more free volume.^{59,72} Accordingly, restoring the segmental symmetry by the introduction of a second aromatic substituent might increase T_g ,⁷² emphasizing the potential of bio-bisphenols derived of di-substituted phenols (*e.g.*, syringol). Moreover, the presence of the *o*-methoxy groups decreased the PC's thermal stability, showing a 29 °C lower maximal degradation temperature (T_{max}) and 15% lower char yield at 600 °C (Table 2, Fig. 4).⁵⁹

Looking into the functionality of the *m,p'*-isomer, Koelewijn *et al.* (2019)⁵⁹ showed that (i) the reactivity of the *m,p'*-isomer of BGF (**22**) was similar to *p,p'*-BGF (**2**) in the PC synthesis and (ii) the polymer properties (*i.e.*, amorphous phase, T_g and thermal stability) of *m,p'*-BGF-PC (**22**) and *p,p'*-BGF-PC (**2**) were similar (Table 2, Fig. 4).⁵⁹

Comparing the fossil-based *p,p'*-BPA-PC and *p,p'*-BPF-PC, the influence of the carbon bridge substituent, methylenedioxy bridge *vs.* isopropylidene bridge, could be determined showing a decrease in thermal stability (T_{max}) and T_g by 27 °C and 20 °C, respectively, for *p,p'*-BPF-PC (Table 2).⁵⁹ This decrease in T_g is related to the higher level of rotational freedom of the methylenedioxy bridged bisphenol. Accordingly, it is known that the (steric) isopropylidene bridge imparts rigidity to the polymer chains, restricting the level of rotational freedom.^{59,72}

To evaluate the functionality of *m,m'*-isomers, Chen *et al.* (2015)⁷³ synthesized *m,m'*-BGF-4M-PC (**26**). Reaching a high

molecular weight and polymer yield, a PC with poor solubility in common organic solvents was obtained. Compared to BPA-PC with similar $\bar{M}_w$ this PC showed a 26 °C lower, but still remarkably high, T_g of 122 °C and good thermal stability with $T_{d5\%}$ of 382 °C and T_{max} of 420 °C (Table 2). Unfortunately, this polymer was obtained as a white crystalline polymer, lacking the desired PC transparency, with m.p. of 314 °C.⁷³ To combat the tendency for crystallisation Koelewijn *et al.* (2017)⁵⁴ synthesized PCs of *m,m'*-BGF molecular structures with longer 4-*n*-alkyl chains, *viz.* *m,m'*-BGF-4E-PC (**29**) and *m,m'*-BGF-4P-PC (**30**). Using GPC/SEC to analyse $\bar{M}_w$ and $\bar{D}$, bimodal curves were observed for all PCs. Since *p,p'*-BPA-PC didn't display a shoulder under identical polymerisation conditions, this effect was attributed to macro-cyclization and associated to the *m,m'*-isomer orientation.⁵⁵ Even though white crystalline polymers were obtained, they observed a higher amorphous character, lower T_m (determined by X-ray diffraction and DSC, respectively), lower T_g and higher solubility in CHCl_3 , DCM and THF upon elongating the 4-*n*-alkyl chain (Table 2, Fig. 4). In conclusion, a 4-*n*-propyl chain substituent (i) lowers the tendency to crystallise, and (ii) improves the solubility in common solvents, facilitating downstream processing.⁵⁴

Another interesting PC was synthesized by Harvey *et al.* (2016)⁵⁰ using *p,p'*-BPF-3iP-6M (**16**) as a precursor. This amorphous PC showed a high T_g of 119 °C and thermal stability close to the commercial BPA-PC references, with $T_{d5\%}$ of 421 °C, $T_{d50\%}$ of 490 °C and char yield of 21% at 600 °C (Table 2, Fig. 4).⁵⁰

The use of *p,p'*-DPA (**5**) as PC precursor introduces a free acid functionality in the polymer chain. This resulted in a PC

Table 2 Physical properties and thermal stability of bisphenol based polycarbonates

				Physical properties			Thermal stability ^f									
Ref.	Nr.	Bisphenol	Yield ^b [%]	Phase ^c	Colour	$\bar{M}_w$ [g mol ⁻¹]	$\bar{M}_n$ [g mol ⁻¹]	D	Crystalline	T _m [°C]	T _g ^d [°C]	T _{d5%} [°C]	T _{d10%} [°C]	T _{d50%} [°C]	T _{dmax} [°C]	Char _{600°C} [%]
Commercial polycarbonate references																
64	—	<i>p,p'</i> -BPA	—	Solid	White	Commercial grade	—	—	—	—	—	445	460 ^a	505 ^a	504	25
65	—	<i>p,p'</i> -BPA	—	Solid	White	28 000	16 000	1.8	—	—	—	525 ^a	535 ^a	552 ^a	540	31 ^a
130	—	<i>p,p'</i> -BPA	—	Solid	White	35 000	11 000	3.2	—	—	145	—	—	—	494	—
70	—	<i>p,p'</i> -BPA	—	Solid	White	28 400	13 720	2.1	Yes	220	145	—	—	—	—	—
Synthesized polycarbonate references																
59	—	<i>p,p'</i> -BPA	86	Solid	White	126 000	41 000	3.1	—	—	147	446	456	496	498	20 ^a
59	—	<i>p,p'</i> -BPA	81	Solid	White	16 000	4500	3.6	—	—	134	411	431	474	474	22 ^a
49	—	<i>p,p'</i> -BPA	77 ^a	Solid	—	41 000	20 800	2.0	—	—	148	—	—	—	—	—
59	—	<i>p,p'</i> -BPF	74	Solid	Off-white	—	—	—	—	—	114	402	427	524	447	40 ^a
Polycarbonates from bio-based bisphenols																
59	2	<i>p,p'</i> -BGF	89	Solid	Pale-yellow	23 000	6100	3.8	—	—	106	363	386	422	418	25 ^a
59	22	<i>m,p'</i> -BGF	88	Solid	Pale-yellow	20 000	5700	3.5	—	—	108	361	385	420	417	24 ^a
73	26	<i>m,m'</i> -BGF-4M	83	Solid	White	46 773	—	—	Yes	314	122	382	394	450 ^a	420	21 ^a
54	26	<i>m,m'</i> -BGF-4M	62	Solid	White	—	2503	—	Yes	292–305	125	346	373	415 ^a	422	12 ^a
54	29	<i>m,m'</i> -BGF-4E	65	Solid	White	—	4783	—	Yes	236–273	116	376	392	423 ^a	429	14 ^a
54	30	<i>m,m'</i> -BGF-4P	63	Solid	White	—	5182	—	Yes	205–220	99	360	376	417 ^a	424	5 ^a
50	16	<i>p,p'</i> -BPF-3IP-6M	68 ^a	Solid	White	16 320	10 200	1.6	—	—	119	421	450 ^a	490 ^a	—	21 ^a
74	5	<i>p,p'</i> -DPA	89 ^a	—	—	23 000	15 000	1.5	—	—	147	215 ^a	250 ^a	390 ^a	—	—
49	6	<i>p,p'</i> -DPA-Me	80 ^a	—	—	42 400	21 300	2	—	—	99	350 ^a	375 ^a	445 ^a	—	18 ^a
46	6	<i>p,p'</i> -DPA-Me	95	—	—	30 000–50 000	—	—	—	—	126 ^c	—	—	—	—	—
46	7	<i>p,p'</i> -DPA-Et	95	—	—	30 000–50 000	—	—	—	—	103 ^e	—	—	—	—	—
46	8	<i>p,p'</i> -DPA- <i>n</i> Pr	95	—	—	30 000–50 000	—	—	—	—	96 ^e	—	—	—	—	—
46	9	<i>p,p'</i> -DPA- <i>n</i> Bu	95	—	—	30 000–50 000	—	—	—	—	92 ^e	—	—	—	—	—

^a Data extracted from experimental information, plots or pictures in reference. ^b Theoretical yield mol%. ^c Phase at room temperature (RT). ^d DSC experiments were used to determine the T_g except for ^e softening point defined by author. ^f Thermal degradation determined by TGA under nitrogen atmosphere.

Fig. 4 Polymer properties of the bio-based and reference polycarbonates. Representation of (A) the onset thermal degradation temperature, 5% weight loss temperature ($T_{d5\%}$) under nitrogen atmosphere (B) the temperature of 50% weight loss or $T_{d50\%}$ under nitrogen atmosphere and (C) the glass transition temperature (T_g) of the polycarbonates. The area of the datapoints in the bubble charts are associated to the polymers average $\overline{M}_w$, as indicated in the legend underneath.

with (i) high T_g of 147 °C, induced by hydrogen bonding retarding the local chain motion, but (ii) a relatively low thermal stability, with $T_{d5\%}$ of 215 °C and $T_{d50\%}$ of 390 °C being, respectively, 310 °C and 162 °C lower than commercial BPA-PC with similar $\overline{M}_w$ and D (Table 2).⁷⁴ To enhance compatibility with plasticizers, increase the solubility of the PC and lower T_g , alkyl esters were synthesized from p,p' -DPA (6–9) and used for PC synthesis. Fischer *et al.* (1966)⁴⁶ showed that (i) all DPA-ester PCs were more soluble in organic solvents compared to BPA-PC, and (ii) a decreasing softening point ($\approx T_g$) with increasing alkyl ester (Fig. 4).⁴⁶ In addition Moore and Tannahill (2001)⁴⁹ examined the thermal stability of a p,p' -DPA-Me-PC (6), reporting $T_{d5\%}$ of 350 °C and $T_{d50\%}$ of 445 °C. This PC showed a significantly higher thermal stability than p,p' -DPA-PC (5), hence, the thermal stability increased by esterification of the carboxyl group in p,p' -DPA-PC (5).⁴⁹

Up to 90% of all PCs are produced today by the phosgene process. Unfortunately, this process has some major drawbacks: (i) the high toxicity of phosgene, (ii) the use of large amounts of chlorinated, volatile solvents (*i.e.*, DCM) and (iii) the large quantity of (waste) water.⁶³ Therefore it is worth men-

tioning that Fukuoka *et al.* (2003)⁷⁵ presented a more environmental friendly non-phosgene process to produce PC: the Asahi Kasei process. This new technology uses ethylene oxide, CO₂ and BPA to yield BPA-PC and monoethyleneglycol.⁷⁵

In general, all PCs were found to be amorphous except for the PCs synthesized from the m,m' -isomers. However, it was shown that introduction of 4-alkyl chains in these m,m' -bio-bisphenols lowered the polymer crystallinity. The p,p' -DPA-PC (5) could reach T_g similar to that of p,p' -BPA-PC. This high T_g was induced by hydrogen bonding of the free acid functional groups, limiting the polymer chain's rotational freedom. Furthermore, it was shown that (i) the presence of *o*-methoxy moieties lowers T_g moderately about 8 °C, (ii) the use of m,p' -isomers does not impact PC's T_g , and (iii) the substitution of the isopropylidene bridge with a methyldene bridge lowers T_g about 20 °C. The latter shows the beneficial impact of steric substituents on the carbon bridge which impart rigidity to the polymer chains, restricting the level of rotational freedom. Like for T_g , the thermal stability lowered (i) in the presence of *o*-methoxy groups and (ii) by substitution of the isopropylidene bridge with a methyldene bridge. The thermal stability of the

bio-based PCs was the lowest for *p,p'*-DPA-PC (**5**) with $T_{d5\%}$ of 215 °C and $T_{d50\%}$ of 390 °C and the highest for *p,p'*-BPF-3iP-6M-PC (**16**) with $T_{d5\%}$ of 421 °C and $T_{d50\%}$ of 490 °C.

Even though the current bio-based PCs do not show T_g and thermal stability as high as the BPA-PC references, the PCs show excellent thermomechanical properties suitable for diverse polymer applications. Hence, it is strongly believed that by adopting and expanding the presented structure-property relationships, future molecular bisphenol designs might lead to bio-based PCs reaching or even surpassing the performance of current BPA-based PCs.

3.2 Polyesters

Since 1979, BPA-based polyesters were commercially produced using an interfacial polymerization reaction of BPA and the acid chloride of terephthalic and/or isophthalic acid, being terephthaloyl chloride (TPC) and isophthaloyl chloride (IPC), respectively (Fig. S2b, ESI†). Because of their fully aromatic nature, these polyesters are called polyarylates (PARs).^{76,77} The incorporation of aromatic groups into the polymer chain results in polyesters with (i) high heat resistance, (ii) hydrophobicity (*i.e.*, resistance to hydrolysis⁶⁶), and (iii) high glass transition temperatures (T_g 's), suitable for high-performance applications and widely used as engineering plastics. However, the extremely elevated T_g 's, high melting viscosity and poor solubility hamper polymer processing.^{78–80} Another characteristic of PARs is the polymer gas permeability and selectivity; this is mostly discussed in older research papers concerning PARs.^{81,82}

To assess the polymer properties of the bio-based PARs, two characteristic parameters were selected to be discussed: (i) the glass transition temperature (T_g), and (ii) the thermal stability. Similar to the PCs, the mass-average molecular weight ($\bar{M}_w$) and dispersity ($\mathcal{D}$) impact PARs polymer properties, unfortunately these parameters were not always provided by the authors (Table 3). Besides, it should be mentioned that the molecular structure of the carboxylic acid influences polymer properties. It has been shown that the polymer solubility decreased but the polymer rigidity, and so T_g , increased using TPC instead of IPC.⁸¹ Accordingly, T_g of a PAR from BPA and TPC, *p,p'*-BPA-PAR_{TPC}, ranges from 190 °C to 230 °C,^{55,76,81–83} whereas for a PAR from BPA and IPC, *p,p'*-BPA-PAR_{IPC}, T_g of 180 °C is reported.^{81,82} In addition, both PARs show similar thermal stability, with $T_{d5\%}$ above 450 °C, $T_{d50\%}$ above 500 °C and char yield at 600 °C of 30%. Moreover, Korshak *et al.* (1965)⁸⁴ reported a similar thermal stability and softening point ($\approx T_g$) for *p,p'*-BPA and *p,p'*-BPF based PARs.⁸⁴ The bisphenols used for the syntheses of PARs and their mutual structural relations are shown in Fig. 5. All collected data concerning the polyesters and their polymer properties are summarized in Table 3 and Fig. 6.

Curia *et al.* (2018)⁷⁸ used a mixture of BGF regioisomers (2-21-22) and TPC to synthesize a (partially) bio-based PAR, *mix'*-BGF-PAR_{TPC}. The PAR of *mix'*-BGF showed high molecular weight, high T_g of 164 °C and good thermal stability with $T_{d5\%}$ of 387 °C and $T_{d50\%}$ of 500 °C. Although lower than *p,p'*-

Table 3 Physical properties and thermal stability of bisphenol based polyesters

Physical properties										Thermal stability ^e						
Ref.	Nr.	Bisphenol	Yield ^b [%]	Phase ^c	Colour	$\bar{M}_w$ [g mol ⁻¹]	$\bar{M}_n$ [g mol ⁻¹]	$\bar{D}$	Crystalline	T_m [°C]	T_g^d [°C]	$T_{d5\%}$ [°C]	$T_{d10\%}$ [°C]	$T_{d50\%}$ [°C]	T_{dmax} [°C]	Char _{600°C} [%]
Synthesized polyester reference – terephthaloyl chloride																
55	—	<i>p,p'</i> -BPA	>90	Solid	White	47 300	—	—	Yes	362	226	455	474 ^a	521 ^a	506 ^a	33 ^a
Synthesized polyester reference – isophthaloyl chloride																
79	—	<i>p,p'</i> -BPA	—	—	—	—	—	—	—	—	180	465 ^a	480 ^a	510 ^a	—	30 ^a
Polyester from bio-based bisphenols – terephthaloyl chloride																
78	2–21–22	<i>mix'</i> -BGF	89	Solid	Pale-yellow ^a	61 870	26 900	2.3	—	—	164	387	401 ^a	500 ^a	419	40 ^a
55	31	<i>m,m'</i> -BSF-4M	>90	Solid	Pale-yellow ^a	20 400	6300	3.2	—	—	186	362	376 ^a	431 ^a	395 ^a	21 ^a
55	32	<i>m,m'</i> -BSF-4P	>90	Solid	Off-white ^a	43 000	24 400	1.8	—	—	157	345	363 ^a	407 ^a	388 ^a	11 ^a
Polyester from bio-based bisphenols – isophthaloyl chloride																
79	5	<i>p,p'</i> -DPA	—	—	—	—	—	—	—	—	159	260 ^a	280 ^a	441 ^a	—	25 ^a
79	6	<i>p,p'</i> -DPA-Me	—	—	—	—	—	—	—	—	149	380 ^a	400 ^a	460 ^a	—	26 ^a
79	7	<i>p,p'</i> -DPA-Et	—	—	—	—	—	—	—	—	140	380 ^a	402 ^a	485 ^a	—	38 ^a

^a Data extracted from experimental information, plots or pictures in reference. ^b Theoretical yield mol%. ^c Phase at room temperature (RT). ^d DSC experiments were used to determine the T_g .

^e Thermal degradation determined by TGA under nitrogen atmosphere.

Fig. 5 Bio-bisphenols used for the synthesis of polyesters. The representation of so far reported bio-bisphenols, in addition to the petroleum-based references, used for the synthesis of (partially) bio-based polyesters using terephthaloyl chloride (TPC) and partially bio-based polyesters using isophthaloyl chloride (IPC) and their structural relations.

Fig. 6 Polymer properties of the bio-based and reference polyesters. Representation of (A) the onset thermal degradation temperature, 5% weight loss temperature ($T_{d5\%}$) under nitrogen atmosphere (B) the temperature of 50% weight loss or $T_{d50\%}$ under nitrogen atmosphere and (C) the glass transition temperature (T_g) of the polyesters. The area of the data points in the bubble charts are associated to the polymers average $\overline{M}_w$ as indicated in the legend below the set of graphics. Left: TPC-based polyesters; Right: IPC-based polyesters.

BPA-PAR_{TPC} and *p,p'*-BPF-PAR_{TPC}, these are excellent polymer properties suitable for high-performance applications.⁷⁸ Koelewijn *et al.* (2018)⁵⁵ synthesized PARs from *m,m'*-bisyringols: *m,m'*-BSF-4M (31) and *m,m'*-BSF-4P (32) using TPC. Similar to the polycarbonates of *m,m'*-isomers, the *m,m'*-BSF-4M-PAR_{TPC} (31) and *m,m'*-BSF-4P-PAR_{TPC} (32) showed high $\bar{M}_w$, but also a bimodal $\bar{M}_w$ distribution indicating the presence of macrocycle polymer chains. However, amorphous PARs with high T_g (157–186 °C), and good thermal stability, with $T_{d5\%} \geq 345$ °C and $T_{d50\%} \geq 407$ °C (Table 5, Fig. 6) were obtained.⁵⁵ Moreover, *mix'*-BGF-PAR_{TPC} (2-21-22), *m,m'*-BSF-4M-PAR_{TPC} (31) and *m,m'*-BSF-4P-PAR_{TPC} (32) showed to be soluble in common organic solvents, advancing its usefulness and processability (*e.g.*, coating, casting, spinning).⁷⁸

The PAR synthesized from *p,p'*-DPA (5) and IPC, *p,p'*-DPA-PAR_{IPC} (5), showed T_g of 159 °C, only 20 °C lower than that of *p,p'*-BPA-PAR_{IPC}. However, similar to the polycarbonate from *p,p'*-DPA, *p,p'*-DPA-PAR_{IPC} was characterised by a lower thermal stability, showing $T_{d5\%}$ of 260 °C and $T_{d50\%}$ of 441 °C.⁸⁵ To enhance the thermal stability, Ping *et al.* (2009)⁷⁹ used methyl and ethyl esters (6–7) for the synthesis of PARs. $T_{d5\%}$ of *p,p'*-DPA-Me-PAR_{IPC} (6) and *p,p'*-DPA-Et-PAR_{IPC} (7) was found to be 120 °C higher than that of *p,p'*-DPA-PAR_{IPC} (5), suggesting a significant increase of the thermal stability through the use of *p,p'*-DPA-esters. T_g lowered upon esterification and with the elongation of the alkyl chain, being 149 °C and 140 °C for *p,p'*-DPA-Me-PAR_{IPC} (6) and *p,p'*-DPA-Et-PAR_{IPC} (7), respectively (Table 3, Fig. 6).⁷⁹

The three main parameters controlling gas permeation in PARs are packing density, chain rigidity and molecular mobility. Hence, substitution on the DPM bisphenol core structure directly influences gas permeability and selectivity of the polymer matrix.⁸¹ In this regard, Charati *et al.* (1992)⁸⁶ and Kharul *et al.* (1998)⁸¹ showed that the permeability and selectivity of the polymer matrix can be modified and improved by (i) bulkier alkyl substituents on the bisphenols carbon bridge⁸⁶ and (ii) *o*-methylation of bisphenol.⁸¹ Although not studied yet, this indicates high potential features of the here presented new bio-based PARs.

In order to prepare entirely renewable PARs, the fossil-based TPC and IPC might be substituted by the acyl dichloride of 2,5-furandicarboxylic acid (FDCA) (Fig. S2b, ESI†).⁸⁷ FDCA is derived from a first generation furan derivative, HMF, which is synthesized from mono- and polysaccharides.⁸⁸ In this regard, Curia *et al.* (2018)⁷⁸ synthesized a fully bio-based polyester from *mix'*-BGF (2-21-22) and the dichloride of FDCA, *mix'*-BGF-PAR_{FDCA} (2-21-22). The use of the dichloride of FDCA instead of TPC, lowered T_g by 7 °C, $T_{d5\%}$ by 41 °C and $T_{d50\%}$ by 100 °C. With T_g of 157 °C, $T_{d5\%}$ of 346 °C and $T_{d50\%}$ of 400 °C, this polymer still shows excellent polymer properties for valuable engineering applications.⁷⁸

Similar to the PC, the PAR of *p,p'*-DPA (5), *p,p'*-DPA-PAR_{IPC} (5), could reach a T_g the closest to the BPA-based reference, being only 20 °C lower than the T_g of *p,p'*-BPA-PAR_{IPC}. In addition, T_g of the PARs lowered by (i) the presence of *o*-methoxy moieties and/or (ii) the use of *m,m'*-bisphenol

isomers and/or (iii) the presence of 4-alkyl chains and (iv) the incorporation of ester functional groups (*cf.* *p,p'*-DPA-PAR_{IPC} (5)). The thermal stability of the bio-based PARs was the lowest for *p,p'*-DPA-PAR_{IPC} (5) with $T_{d5\%}$ of 260 °C and $T_{d50\%}$ of 447 °C and the highest for *mix'*-BGF-PAR_{TPC} (2-21-22) with $T_{d5\%}$ of 387 °C and $T_{d50\%}$ of 500 °C. Moreover, the bio-based polyesters, *viz.* *mix'*-BGF-PAR_{TPC} (2-21-22), *m,m'*-BSF-4M-PAR_{TPC} (31) and *m,m'*-BSF-4P-PAR_{TPC} (32), showed to be soluble in common organic solvents. This is in contrast to the current petroleum-based PARs, for which poor solubility and elevated T_g 's (>200 °C) hamper polymer processing. This emphasizes the potential of the current, and future bio-bisphenol alternatives, yielding polyesters with lower, but still remarkably high, T_g 's (*i.e.*, ≥ 157 °C) combined with good solvent solubility.

3.3 Epoxy resins

Since 1946, Bisphenol A diglycidyl ether or BADGE is commercially manufactured through the coupling of BPA and epichlorohydrin in the caustic coupling or the phase-transfer catalyst process (Fig. S2c, ESI†). Over time, the market of epoxy resins (ERs) has been growing continuously. Using different formulations, composites or derivatives of ERs (*e.g.*, vinyl ester resins), a plethora of materials with diverse properties has been developed to answer specific needs in upcoming industries (*e.g.*, electronic industry, wireless phones, waterborne coatings, windmill blades).^{3,77,89} Today, ERs are an important class of industrial polymers, from which 75% is derived of BADGE.³ Pure BADGE is a white solid with a melting point of 43 °C and it has an epoxide equivalent weight (EEW) of 170 g eq.⁻¹ EEW is defined by the molecular weight of the resin for one equivalent of epoxide, glycidyl ether. Hence, EEW of an epoxy resin (ER) increases if a resin contains dimers, trimers or oligomers. The deviation of EEW from the theoretical EEW (*i.e.* EEW of the pure diglycidyl monomer) is indicated by the degree of polymerization (n).³ Most commercial BADGE resins show higher EEW; for instance Epon 828 is a liquid resin with 190 g eq.⁻¹ EEW and n equal to 0.14.⁵⁸

A hardener or curing agent is added to the epoxy resin to cross-link the resin yielding a resilient thermosetting polymer or thermoset. A variety of curing reagents can be used to target specific polymer properties. In general, the most important group of curing agents contains active hydrogen atoms (*e.g.*, primary and secondary amines, phenols, carboxylic acids). Low molecular weight aliphatic amines, like diethylenetriamine (DETA), are used to obtain tightly cross-linked resins with good physical properties, chemical and solvent resistance but limited toughness and thermal stability. To improve toughness and thermal stability, cycloaliphatic amines can be used as curing agents, such commercial curing agents are isophorone diamine (IPDA) and bis(4-aminocyclohexyl)methane (PACM). Moreover, T_g of the thermoset is elevated up to 150 °C using cycloaliphatic curing agents. A further enhancement of thermal stability and chemical resistance can be acquired using aromatic amines as curing agents. For instance methylenedianiline (MDA), a widely used curing

agent, provides in addition excellent mechanical and electrical properties to the thermoset.³

Industrially, thermoset resins, for instance formulations of the epoxy resin and curing agent (*i.e.*, composites, if inorganic fillers are added), are cured at elevated temperatures (155–200 °C) by compression or injection moulding. In the latter process the melt temperature inside the plasticizing cylinder is considered in the range of 55 to 115 °C.⁶⁷ Therefore, the phase at RT, viscosity and cure kinetics of the formulated resins are interesting parameters to evaluate the processability of the composite. Unfortunately, the phase at RT and viscosity of the formulation are rarely reported in research papers concerning new bio-based ERs, therefore, the processability of the formulation is assessed by its cure kinetics. In general, the curing reaction of a thermoset resin is exothermic. Hence, the cure kinetics might be examined by DSC. In most studies a dynamic DSC scan, with a heating ramp of 10 °C min⁻¹, is used to determine (i) the onset cure temperature (T_i), and (ii) the peak exotherm temperature (T_p), the temperature where the maximal polymerisation rate is achieved. However, more in-depth insights into the cure kinetics can be achieved by (i) isothermal and/or (ii) varying heating ramp DSC experiments.⁹⁰

BADGE is readily used in thermoset resin formulations to acquire high-performance thermosets. In general, BADGE thermosets are characterised by their mechanical strength, chemical resistance and thermal stability.^{2,3} Therefore, the three parameters taken into account to evaluate the potential of today's bio-based ERs are (i) the storage modulus (E'), (ii) T_g and (iii) thermal stability. The storage modulus E' is determined by DMA experiments and reflects the amount of stored energy in a viscoelastic material, hence, a measure of the solid character of the material. E' is strongly related to the present molecular motions, when determined at lower temperatures (*i.e.*, 25 °C, 30 °C or 45 °C) in the glassy state of a polymer. This parameter provides more information about chain packing and molecular interactions.^{58,91} Crossing the glass transition temperature upon heating, E' drops as molecular motions are induced. In general, E' determined at 30 °C above T_g is associated to the rubbery state of the polymer, and according to the rubber elasticity theory, inversely proportional to the molecular weight between cross-links (M_x) and therefore directly proportional to the cross-link density.^{60,91} Noteworthy, just like the $\bar{M}_w$ influences thermoplastic polymer properties, the cross-link-density or degree of cross-linking influences the final thermosetting polymer properties. As the cross-link density of the sample increases, the molecular motions in the polymer are restricted and T_g rises.⁹¹ Despite its importance, the cross-link density is seldom reported, rather, related parameters *via* the rubber elasticity theory are given. To include this aspect in the analysis, these parameters were summarized in Table 5. As the degree of cross-linking rises, strength and rigidity increases, whereas elongation capacity decreases.⁶⁶

It is clear that different aspects (*e.g.*, formulation, cure protocol) influence the processability and the final polymer properties. Consequently, the extraction of relevant structure-

property relations is limited to similar formulations and cross-link density. The bio-bisphenols used for the syntheses of ERs and their mutual structural relations are shown in Fig. 7. All collected data concerning the uncured and cured ERs are summarized in Tables 4, 5 and Fig. 8.

In addition to BPA, BPF is used to manufacture BFDGE, showing a slightly higher reactivity and lower viscosity than BADGE commercial resins.³ This BFDGE often exists as a mixture of regioisomers, *mix'*-BPF-DGE, with *o,p'*-BPF-DGE as the dominant isomer.⁹² Hence, the lower viscosity of a commercial BFDGE resin is conveyed by (i) the methylene bridge and/or (ii) the presence of *ortho*-regioisomers.⁴² In this regard, Hernandez *et al.* (2016)⁵⁸ synthesized the epoxy resin (ER), or diglycidyl ether (DGE), of *mix'*-BGF (2-21-22), abbreviated as *mix'*-BGF-DGE. This highly pure resin ($n = 0.04$) was obtained as a white solid with 112–114 °C m.p. *mix'*-BGF-DGE (2-21-22) showed to be miscible with PACM and was found highly reactive yielding a high degree of cure (>99%). T_g of the *mix'*-BGF-DGE_{PACM} (2-21-22) thermoset (111 °C) showed to be lower than T_g 's observed for the commercial reference thermosets BADGE_{PACM} (*i.e.*, Epon 828_{PACM}) and BFDGE_{PACM} (*i.e.*, Epon 862_{PACM}) with 158 °C and 138 °C T_g , respectively (Table 5, Fig. 8). This decrease in T_g can be ascribed to an increase of the degree of rotational freedom caused by (i) the methylene bridge and (ii) the *o*-methoxy groups. The *mix'*-BGF-DGE_{PACM} (2-21-22) thermoset showed a good thermal stability with $T_{d5\%}$ of 363 °C and T_{max} of 376 °C, both being only 16 °C lower than the BADGE_{PACM} reference. Interestingly, the *mix'*-BGF-DGE_{PACM} (2-21-22) thermoset showed a higher storage modulus at 25 °C (E'_{25}) and glassy modulus than the reference BADGE_{PACM} (Epon 828_{PACM}) and BFDGE_{PACM} (Epon 862_{PACM}) thermosets (Table 5, Fig. 8). The authors related this increase in E'_{25} to the presence of the *o*-methoxy groups, inducing hydrogen bonding interactions between the *o*-methoxy moieties and the hydroxyl groups formed by the epoxy-amine cure reaction.⁵⁸

To attain more insight into the influence of *o*-methoxy moieties in the DPM core structure on ERs thermoset properties, Nicastro *et al.* (2018)⁶⁰ synthesized ERs derived from *o,p'*-GPF (20), *p,p'*-GPF (1), *m,p'*-GSF (23), *p,p'*-GSF (3), *m,p'*-BSF (24) and *p,p'*-BSF (4), and mixtures thereof (1-20), (3-23) and (4-24), using the aromatic diamine MDA. All ERs, except the commercial references BADGE and BFDGE and *m,p'*-BSF-DGE (24), show a high monomer purity with a degree of polymerization ranging from 0.01 to 0.04. A first interesting observation was made comparing the physical appearance of the different regioisomers. All ERs derived from *p,p'*-isomers were solids with m.p. up to 115 °C; the lowest m.p. was observed for *p,p'*-GPF-DGE (1) being 52 °C. Adding *o*-methoxy moieties to the bisphenol structures clearly increased the resins m.p., as *p,p'*-GSF-DGE (3) and *p,p'*-BSF-DGE (4) showed m.p. of 64 °C and 115 °C, respectively (Table 4). In contrast, the ERs of the *o,p'*-isomer and *m,p'*-isomers were liquid at RT. This indicates that (i) the amount of *o*-methoxy moieties and (ii) isomer orientation of the bisphenol significantly influences ER's m.p. In addition to the pure ERs, ERs of the regioisomer mixtures obtained after reaction were synthesized. These ERs showed to

Fig. 7 Bio-bisphenols used for the synthesis of epoxy resins. The representation of so far reported bio-bisphenols, in addition to the petroleum-based references, used for the synthesis of epoxy resins and the curing agents used for formulations thereof. The curing agents are diethylenetriamine (DETA), isophorone diamine (IPDA), bis(4-aminocyclohexyl)methane (PACM), methylenedianiline (MDA) and Pripol 1040.

be solid for *mix'*-GPF-DGE (**1-20**) and *mix'*-BSF-DGE (**4-24**), liquid for *mix'*-GSF-DGE at RT (**3-23**).⁶⁰

All ERs were miscible with MDA except for *mix'*-BGF-DGE (**2-21-22**), therefore the latter is not further discussed, the former showed full conversions after curing. Although not discussed by the authors, some additional information about the resins processability (*i.e.*, phase at RT, m.p. of the formulation and cure kinetics) can be derived from a dynamic DSC cure experiment, given that the epoxy-amine curing reaction is exothermic. Firstly, all formulations of *mix'*-ERs were liquid at RT. Secondly, the onset cure temperature (T_i) was similar for all bio-based epoxy resins and bisphenol reference resins (*i.e.*, 50–60 °C). Thirdly, the peak exotherm temperature (T_p), showed the following order: *mix'*-GPF-DGE_{MDA} (**1-20**) with 140 °C < *mix'*-BFDGE_{MDA} with 142 °C < *p,p'*-BADGE_{MDA} with 148 °C < *mix'*-GSF-DGE_{MDA} (**3-23**) with 150 °C < *mix'*-BSF-DGE_{MDA} (**4-24**) with 152 °C (Table 4).⁶⁰ Because of their different regioisomer composition, the influence of *o*-methoxy moieties on cure kinetics and reactivity cannot be determined. However, these results indicate that the processability of all *mix'*-ERs is similar to the references, BADGE_{MDA} and BFDGE_{MDA}.

The storage moduli at 200 °C (E'_{200}), rubbery modulus, and T_g were higher for all ERs derived from *p,p'*-isomer bisphenol structures compared to the ERs derived from *m,p'*- or *o,p'*-isomers (Table 5, Fig. 8). Hence, the ERs derived from the *p,p'*-isomer achieve a higher cross-link density during cure, increas-

ing T_g of the cured resin. The author accounts this difference to the presence of topological cyclic defects in the polymer networks derived from *o,p'*- and *m,p'*-isomer ERs.^{60,93} In general, T_g of the thermosets decreased with increasing amount of *o*-methoxy moieties. It was hypothesized that additional *o*-methoxy groups hinder close chain packing, resulting in lower T_g 's. However, *p,p'*-BSF-DGE (**24**) showed a high T_g of 141 °C comparable to T_g 's of the GPF-DGE (**20, 1, 1-20**) thermosets ranging from 132 °C to 151 °C, indicating that a fourth *o*-methoxy group hinders the chain mobility and increases chain packing (Fig. 8). Furthermore, there was no significant difference observed for the glassy modulus at 30 °C (E'_{30}) of all bio-based and reference ERs.⁶⁰

Finally, it was shown that the increasing amount of *o*-methoxy groups decreases the thermal stability of the cured resin. This was expected as methoxy groups *ortho* to the glycidyl ether linkage reduce the thermal energy required for homolytic cleavage of the phenoxy-glycidyl bond.^{60,94} Even though, the thermal stability of the bio-based ERs is high enough ($T_{d5\%} > 344$ °C) for applications in food can linings and structural adhesives.⁶⁰

In 2016, Zhao *et al.*⁵⁷ presented the ER of *m,m'*-BGF-4P (**30**), *m,m'*-BGF-4P-DGE (**30**). Using an aliphatic amine, DETA, as curing agent the thermoset *m,m'*-BGF-4P-DGE_{DETA} (**30**) was obtained. Looking into the cure kinetics, an activation energy (E_a) of cure of 46 kJ mol⁻¹ was observed, T_i of 51 °C and T_p of 92 °C (Table 4). The thermoset showed a cross-link density of

Table 4 Physical properties of uncured epoxy resins and curing reactivity

Ref.	Nr.	Bisphenol	Isomer distribution	Yield ^b [%]	Physical properties uncured resin			Curing – reactivity			
					EEW [g eq. ⁻¹]	<i>n</i>	Phase ^c Colour	<i>T</i> _m [°C]	<i>T</i> _i ^d [°C]	<i>T</i> _p ^d [°C]	<i>H</i> _r ^d [kJ eq. ⁻¹]
Curing reagent: Amicure PACM											
58	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	190	0.14	Liquid	—	—	—	—
58	—	<i>mix'</i> -BPF	<i>o,o'</i> -14%; <i>o,p'</i> -49%; <i>p,p'</i> -37%	—	170	0.13	Liquid	—	—	—	—
58	2-21-22	<i>mix'</i> -GGF	<i>o,p'</i> -3%; <i>m,p'</i> -15%; <i>p,p'</i> -82%	—	193	0.04	Solid	White	112-114	—	—
Curing reagent: MDA											
60	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	186	0.11	Liquid	—	50-60 ^a	148 ^a	128
60	—	<i>mix'</i> -BPF	<i>o,o'</i> -14%; <i>o,p'</i> -49%; <i>p,p'</i> -37%	—	169	0.10	Liquid	—	50-60 ^a	142 ^a	112
60	20	<i>o,p'</i> -GPF	<i>o,p'</i> -100%	75-80	176	0.03	Liquid	—	—	—	—
60	1	<i>p,p'</i> -GPF	<i>p,p'</i> -100%	75-80	174	0.02	Solid	—	52	—	—
60	1-20	<i>mix'</i> -GPF	<i>o,p'</i> -19%; <i>p,p'</i> -81%	75-80	172	0.01	Solid	—	44	140 ^a	124
60	2-21-22	<i>mix'</i> -BGF	<i>o,p'</i> -2%; <i>m,p'</i> -18%; <i>p,p'</i> -80%	75-80	189	0.02	Solid	—	113	132 ^a	—
60	23	<i>m,p'</i> -SGF	<i>m,p'</i> -100%	75-80	204	0.02	Liquid	—	—	—	—
60	3	<i>p,p'</i> -SGF	<i>p,p'</i> -100%	75-80	208	0.04	Solid	—	64	—	—
60	3-23	<i>mix'</i> -SGF	<i>m,p'</i> -79%; <i>p,p'</i> -21%	75-80	201	0	Liquid	—	50-60 ^a	150 ^a	119
60	24	<i>m,p'</i> -BSF	<i>m,p'</i> -100%	75-80	249	0.17	Liquid	—	—	—	—
60	4	<i>p,p'</i> -BSF	<i>p,p'</i> -100%	75-80	219	0.02	Solid	—	115	—	—
60	4-24	<i>mix'</i> -BSF	<i>m,p'</i> -76%; <i>p,p'</i> -24%	75-80	220	0.02	Solid	—	75	152 ^a	92
Curing reagent: DETA											
95	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	—	—	—	—	—	—	—
96	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	189	—	Liquid	—	—	—	—
57	30	<i>m,m'</i> -BGF-4P	<i>m,m'</i> -100%	—	—	—	—	—	51	92	46
57	14	<i>p,p'</i> -BCF-3P	<i>p,p'</i> -100%	—	—	—	—	—	43	82	44
52	12	<i>p,p'</i> -BCF _{UR} -3M	<i>p,p'</i> -100%	49	—	—	Liquid	Reddish-brown	20 ^a	79	—
52	13	<i>p,p'</i> -BCH _{MIF} -3M	<i>p,p'</i> -100%	33	—	—	Liquid	Reddish-brown	20 ^a	73	—
Curing reagent: Pripol 1040											
97	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	—	—	—	—	—	—	—
61	15	<i>p,p'</i> -GCF-3M	<i>p,p'</i> -100%	80-91	186	0.05 ^a	Liquid	Yellowish	—	—	—
Curing reagent: IPDA											
48	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	175	0.04 ^a	Liquid	—	—	—	—
48	6	<i>p,p'</i> -DPA-Me	<i>p,p'</i> -100%	85-97	215	0.05 ^a	Liquid	Pale-yellow	—	—	—
48	7	<i>p,p'</i> -DPA-Et	<i>p,p'</i> -100%	85-97	222	0.05 ^a	Liquid	Pale-yellow	—	—	—
48	9	<i>p,p'</i> -DPA- <i>n</i> Bu	<i>p,p'</i> -100%	85-97	243	0.08 ^a	Liquid	Pale-yellow	—	—	—
48	10	<i>p,p'</i> -DPA- <i>n</i> Pent	<i>p,p'</i> -100%	85-97	265	0.15 ^a	Liquid	Pale-yellow	—	—	—

^a Data extracted from experimental information, plots or pictures in reference. ^b Theoretical yield, %. ^c Phase at room temperature (RT). ^d Dynamic DSC scan(s) to determine the onset of cure (*T_i*), the peak exotherm temperature (*T_p*), the heat of polymerization (*H_r*) and the cure activation energy (*E_{a,cure}*).

Table 5 Physical properties and thermal stability of cured epoxy resins

Physical properties				Thermal stability ^e												
Ref	Nr.	Bisphenol	Isomer distribution	Cross-link density ^b			E'									
				Parameter	Unit	Value	T _g ^c [°C]	[GPa]	[°C]	T _{d5%} [°C]	T _{d10%} [°C]	T _{d50%} [°C]	T _{dmax} [°C]	Char _{600°C} [%]		
Curing reagent: Amicure PACM																
58	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	—	—	158	2.4	25	379	390 ^a	410	392	2		
58	—	<i>mix'</i> -BPF	<i>o,o'</i> -14%; <i>o,p'</i> -49%; <i>p,p'</i> -37%	—	—	—	138	2.6	25	371	390 ^a	410	388	1		
58	2-21-22	<i>mix'</i> -BGF	<i>o,p'</i> -3%; <i>m,p'</i> -15%; <i>p,p'</i> -82%	—	—	—	111	3.4	25	363	375 ^a	392	376	6		
Curing reagent: MDA																
60	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	E' ₂₀₀	[MPa]	46	167	2.5	30	381	385 ^a	405 ^a	398 ^a	24 ^a		
60	—	<i>mix'</i> -BPF	<i>o,o'</i> -14%; <i>o,p'</i> -49%; <i>p,p'</i> -37%	E' ₂₀₀	[MPa]	31	138	2.4	30	375	380 ^a	415 ^a	387 ^a	15 ^a		
60	20	<i>o,p'</i> -GPF	<i>o,p'</i> -100%	E' ₂₀₀	[MPa]	22	141	2.8	30	—	—	—	—	—		
60	1	<i>p,p'</i> -GPF	<i>p,p'</i> -100%	E' ₂₀₀	[MPa]	46	151	2.5	30	—	—	—	—	—		
60	1-20	<i>mix'</i> -GPF	<i>o,p'</i> -19%; <i>p,p'</i> -81%	E' ₂₀₀	[MPa]	43	132	2.7	30	368	376 ^a	401 ^a	385 ^a	25 ^a		
60	2-21-22	<i>mix'</i> -BGF	<i>o,p'</i> -2%; <i>m,p'</i> -18%; <i>p,p'</i> -80%	—	—	—	—	—	—	—	—	—	—	—		
60	23	<i>m,p'</i> -SGF	<i>m,p'</i> -100%	E' ₂₀₀	[MPa]	28	129	2.4	30	—	—	—	—	—		
60	3	<i>p,p'</i> -SGF	<i>p,p'</i> -100%	E' ₂₀₀	[MPa]	33	134	2.7	30	—	—	—	—	—		
60	3-23	<i>mix'</i> -SGF	<i>m,p'</i> -79%; <i>p,p'</i> -21%	E' ₂₀₀	[MPa]	33	113	3	30	359	374 ^a	395 ^a	375 ^a	22 ^a		
60	24	<i>m,p'</i> -BSF	<i>m,p'</i> -100%	E' ₂₀₀	[MPa]	15	119	2	30	—	—	—	—	—		
60	4	<i>p,p'</i> -BSF	<i>p,p'</i> -100%	E' ₂₀₀	[MPa]	26	141	2.5	30	—	—	—	—	—		
60	4-24	<i>mix'</i> -BSF	<i>m,p'</i> -76%; <i>p,p'</i> -24%	E' ₂₀₀	[MPa]	22	111	3.2	30	344	365 ^a	380 ^a	374 ^a	22 ^a		
Curing reagent: DETA																
95	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	—	—	137	2.6	45	—	—	—	—	—		
96	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	—	—	146	—	—	340 ^a	342 ^a	375 ^a	—	8 ^a		
57	30	<i>m,m'</i> -BGF-4P	<i>m,m'</i> -100%	ρ	[mol dm ⁻³]	1.4	70	0.6	30	235	300 ^a	351	—	11		
57	14	<i>p,p'</i> -BCF-3P	<i>p,p'</i> -100%	ρ	[mol dm ⁻³]	3.3	84	1.4	30	245	308 ^a	361	—	11		
52	12	<i>p,p'</i> -BCF _{UR} -3M	<i>p,p'</i> -100%	—	—	—	100	6.6	45	174	270 ^a	362	—	24 ^a		
52	13	<i>p,p'</i> -BCH _{MF} -3M	<i>p,p'</i> -100%	—	—	—	110	9.6	45	214	270 ^a	381	—	29 ^a		
Curing reagent: Pripol 1040																
97	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	—	—	—	25	—	—	—	—	—	—	—		
61	15	<i>p,p'</i> -GCF-3M	<i>p,p'</i> -100%	ρ	[mol dm ⁻³]	2.29	38	—	—	354	398 ^a	470 ^a	—	16 ^a		
Curing reagent: IPDA																
48	—	<i>p,p'</i> -BPA	<i>p,p'</i> -100%	M _x	[g mol ⁻¹]	2330	165 ^d	2.6	25	360 ^a	378	399	—	11		
48	6	<i>p,p'</i> -DPA-Me	<i>p,p'</i> -100%	M _x	[g mol ⁻¹]	1600	158 ^d	3.3	25	352 ^a	361	416	—	13		
48	7	<i>p,p'</i> -DPA-Et	<i>p,p'</i> -100%	M _x	[g mol ⁻¹]	1550	136 ^d	2.2	25	352 ^a	363	403	—	12		
48	9	<i>p,p'</i> -DPA- <i>n</i> Bu	<i>p,p'</i> -100%	M _x	[g mol ⁻¹]	2660	96 ^d	2.2	25	350 ^a	363	406	—	11		
48	10	<i>p,p'</i> -DPA- <i>n</i> Pent	<i>p,p'</i> -100%	M _x	[g mol ⁻¹]	2520	86 ^d	2.1	25	348 ^a	362	400	—	10		

^a Data extracted from experimental information, plots or pictures in reference. ^b Different parameters referring to the cross-link density [mol cm⁻³] according to the rubber elasticity theory. ^c DMA experiments were used to determine the glass transition temperature (T_g) defined by the maximum of $\tan(\delta)$. ^d DMA experiments were used to determine the glass transition temperature (T_g) defined by the peak of the loss modulus. ^e Thermal degradation determined by TGA under nitrogen atmosphere.

Fig. 8 Polymer properties of the bio-based and reference cured epoxy resins. Representation of (A) the onset thermal degradation temperature, 5% weight loss temperature ($T_{d5\%}$) under nitrogen atmosphere (B) the temperature of 50% weight loss or $T_{d50\%}$ under nitrogen atmosphere (C) the glass transition temperature (T_g) and (D) Storage moduli E' at temperature 25 °C–30 °C–45 °C of the cured epoxy resins. The area of the data points in the bubble chart is related to the temperature at which E' is defined. The epoxy resins are divided in sections according to the curing agent used from left to right: PACM, MDA, DETA, Pripol 1040 and IPDA.

1.39 mol dm^{-1} ,³ with T_g of 70 °C, low E'_{30} of 0.6 GPa and thermal stability showing $T_{d5\%}$ of 235 °C and $T_{d50\%}$ of 351 °C (Table 5).⁵⁷ These lower thermomechanical properties, compared to the previously discussed ERs, were expected as an aliphatic curing agent was used. The reference resin BADGE_{DETA} shows a significant higher T_g of 137 °C, E'_{45} of 2.6 GPa and thermal stability with $T_{d5\%}$ of 340 °C and $T_{d50\%}$ of 375 °C.⁹⁵ This might be caused by structural difference due to (i) the isomer orientation, (ii) the methylened bridge and (iii) the 4-alkyl chain.

To further enhance the thermomechanical properties, Zhao *et al.* (2016)⁵⁷ *o'*-demethylated *m,m'*-BGF-4P (30) to obtain a bisphenol structure characterised by four functional hydroxyl

groups, *p,p'*-BCF-3P (14) resulting in a tetra-epoxide, after glycidylation, with four epoxy groups: *p,p'*-BCF-3P-DGE (14). However, up to 20 mol% of a di-epoxy benzodioxane by-product was observed for *p,p'*-BCF-3P-DGE. Surprisingly, a lower T_i , T_p and E_a , compared to *m,m'*-BGF-4P-DGE_{DETA} (30), were reported for *p,p'*-BCF-3P-DGE_{DETA} (14) being 43 °C, 82 °C and 44 kJ mol⁻¹, respectively. This phenomenon is explained by the catalytic effect of the benzodioxane by-products, including a free hydroxyl group, in the epoxy-amine curing reaction. Remarkably, introducing additional epoxy groups more than doubled, even in the presence of benzodioxane by-products, the thermoset's cross-link density reaching values as high as 3.29 mol dm^{-1} .³ This resulted in a thermoset with higher T_g of

84 °C, an E'_{30} (1.4 GPa) and thermal stability with $T_{d5\%}$ of 245 °C and $T_{d50\%}$ of 361 °C.⁵⁷

Using biscatechols, which have four function hydroxyl groups, Jiang *et al.* (2018)⁵² synthesized p,p' -BCF_{UR}-3M-DGE (12) and p,p' -BCH_{MF}-3M-DGE (13). Similar to p,p' -BCF-3P-DGE (14), di-epoxy benzodioxane by-products were obtained in the synthesis of these ERs. The ratio of di- to tetra-epoxy resins in the reaction mixture was found to be 1 to 1.9 and 1 to 1.2 for p,p' -BCF_{UR}-3M-DGE (12) and p,p' -BCH_{MF}-3M-DGE (13), respectively. Using DETA as curing agents, similar cure exotherms were observed for both resins, indicating a similar reactivity. The slightly lower T_p , about 6 °C, of p,p' -BCH_{MF}-3M-DGE_{DETA} (13) can be attributed to presence of an additional hydroxyl group, accelerating the curing reaction (Table 4). T_g and E'_{45} were found higher for p,p' -BCH_{MF}-3M-DGE_{DETA} (13), being 110 °C and 9.6 GPa than for p,p' -BCF_{UR}-3M-DGE_{DETA} (12), being 100 °C and 6.6 GPa. The author attributes this difference to the presence of the hydroxymethyl group (i) inducing stronger inter chain hydrogen bonding and (ii) less free space, limiting the rotational freedom of the polymer chain.⁵² Compared to the BPA-reference BADGE_{DETA} the obtained epoxy resins showed a 27 °C to 37 °C lower T_g , but a, strikingly, 4 GPa to 7 GPa higher E'_{45} (Table 5). This may be explained by the higher rigidity of the thermoset resins. At least, the thermal stability of both thermosets was reported to be lower than that of BADGE_{DETA} for temperatures under 340 °C, but comparable above this temperature. Moreover, the thermosets showed a higher char yield (*cf.* BPADGE_{DETA}, + 8%) above 24% at 600 °C (Table 5).^{52,96}

A careful comparison between p,p' -BCF-3P-DGE_{DETA} (14), p,p' -BCF_{UR}-3M-DGE_{DETA} (12) and p,p' -BCH_{MF}-3M-DGE_{DETA} (13) indicates that the embedding bulky, aromatic and/or polar groups on the bisphenol carbon bridge may be an effective way to enhance the thermomechanical properties of an epoxy thermoset resin.

Thus, Maiorana *et al.* (2015)⁴⁸ reported the synthesis of ERs from DPA-esters: p,p' -DPA-Me-DGE (6), p,p' -DPA-Et-DGE (7), p,p' -DPA-*n*Bu-DGE (9) and p,p' -DPA-*n*Pent-DGE (10). All resins were liquid at RT with *n*-values ranging from 0.05 to 0.15 and it was shown that the resin's viscosity decreased with elongation of the *n*-alkyl ester. The ERs were cured using isophorone diamine (IPDA), obtaining fully cured thermosets. Based on the average molecular weight between cross-links (M_x), it was concluded that *n*-alkyl side chains did not hinder network formation. All thermosets showed similar storage moduli to BADGE_{IPDA} and T_g in the range of 86 °C to 158 °C (Table 5, Fig. 8). Compared to BADGE_{IPDA}, p,p' -DPA-Me-DGE_{IPDA} (6) showed a 0.7 GPa higher storage modulus and T_g only 7 °C lower, this result is attributed to the presence of 6 mol% of a tri-epoxy by-product inducing a higher cross-link density. T_g of the thermosets decreased with elongation of the *n*-alkyl ester. It is stated that the ester moieties function as internal plasticizers increasing chain mobility. Furthermore, all bio-based resins show a high thermal stability with $T_{d5\%} \geq 348$ °C and $T_{d50\%} \geq 400$ °C, comparable to BADGE_{IPDA} with $T_{d5\%}$ of 360 °C and $T_{d50\%}$ of 399 °C (Table 5, Fig. 8).⁴⁸

In 2019, Zhao *et al.*⁶¹ presented the ER, p,p' -GCF-3M-DGE (15), from the asymmetric bisphenol p,p' -GCF-3M (15). Similar to the other catecholic ERs, a benzodioxane by-product was obtained. The ratio of the by-product (*i.e.*, mono-epoxide) to the ER (*i.e.*, tri-epoxide) could be tuned by controlling the reaction time. The ER containing 36% mono- and 64% tri-epoxide was cured with Pripol 1040, a mixture of tricarboxylic (77 wt%) and dicarboxylic (23 wt%) fatty acids, in the presence of Zn (acac)₂ as catalyst. The obtained p,p' -GCF-3M-DGE_{PRIPOL} thermoset showed good mechanical strength, good solvent resistance, T_g of 38 °C (*i.e.*, 13 °C higher than BADGE_{PRIPOL})⁹⁷ and high thermal stability with $T_{d5\%}$ of 354 °C and $T_{d50\%}$ of 470 °C. Noteworthy, p,p' -GCF-3M as well as the fatty acids can be obtained from renewable compounds, enhancing the overall bio-based content of this thermoset.

The bio-based content of ERs can be further enhanced by (i) the use of epichlorohydrin manufactured from glycerol (*i.e.* GTE-process⁹⁸), commercially available under the tradename Epicerol®⁹⁹ and (ii) the use of a renewable curing agent (*e.g.* fatty acids, anhydrides, furan amines).¹⁰⁰

In general, it was shown that the m.p. of ERs depends on the bisphenol isomer orientation and increases by the introduction of *o*-methoxy groups in the bisphenol DPM core scaffold. T_g increased using p,p' -derived epoxy resins reaching a higher cross-link density and was lowered (i) by the presence of *o*-methoxy moieties and (ii) upon elongation of the ester alkyl chain for ERs derived from p,p' -DPA-esters. The thermal stability of the thermosets decreased by the introduction of (additional) *o*-methoxy moieties, reducing the thermal energy required for homolytic cleavage of the phenoxy-glycidyl bond.^{60,94} Interestingly, an increase of the glassy modulus (*i.e.*, storage modulus at 25 °C, 30 °C or 45 °C) was attributed to (i) the presence of *o*-methoxy moieties, (ii) rigid groups on the carbon bridge and (iii) the presence of polar functional groups (*e.g.*, free hydroxyl groups), limiting the rotational freedom of the polymer chain by, for instance, hydrogen bonding interactions. To conclude, ERs with varying m.p. and colour were obtained using bio-bisphenol precursors, yielding bio-based thermosets with a thermal stability and T_g comparable to, but glassy storage moduli (E') surpassing, fossil-based thermosets.

3.4 Cyanate ester resins

The first syntheses of cyanate esters were reported in the early 1960's. A relevant cyanate ester is BADCy, produced by the reaction of BPA with cyanogen chloride in the presence of a tertiary amine (Fig. S2d, ESI†). Upon heating above 150 °C, these cyanate esters polymerize by cyclotrimerization to form triazine rings, yielding polycyanurates, *i.e.*, cyanate ester resins (CERs).^{77,101} A metal catalyst might be added to lower the cure onset temperature (T_i), albeit compromising its thermal properties.¹⁰² CER thermosets show comparable application potential to epoxy resin thermosets, but they reach even higher thermomechanical properties (*e.g.*, $T_g > 200$ °C) and show high stability in demanding environments (*e.g.*, elevated and cryogenic temperatures, exposure to vacuum, high-energy radiation). Therefore, CERs are mainly used as high-performance

materials for specialized applications (e.g., rocket and spacecraft structures, thermonuclear fusion reactors).^{102,103} Another important cyanate ester, commercially available next to BADCy, is LECy prepared from *p,p'*-BPE. While BADCy is a white solid at RT with a m.p. of 79–82 °C, LECy is a super-cooled liquid at RT with a m.p. of 29 °C, facilitating its processing.^{101,102,104}

Like mentioned in the previous section, the phase at RT, m.p., viscosity and cure kinetics of thermoset resins are useful parameters to assess the resin's processability. In general, CERs are characterised by a processing window, i.e., the difference between m.p. of the pure cyanate ester and the onset of the cure (T_i).

Despite their high thermomechanical stability, CERs are prone to hydrolysis when exposed to hot and wet conditions.^{105,106} The hydrolytic stability of CERs has been studied since the 1980's, investigating the influence of cure conversion and structural modifications on the hydrolytic stability of the ester bonds. In particular, it was shown that (i) a higher conversion, leads to a more 'open' structure, more free volume, enhancing the accessibility of the polar cyanurate oxygens and (ii) the presence of a methyl group in *ortho* to the cyanate group (i.e., *o*-methyl group) moderately enhanced the hydrolytic stability by sterically hindering the cyanurate oxygen, thus, the absorption of water.^{101,103,106} To assess the performance after exposure to wet and hot conditions, T_g of CERs is, generally, determined before and after immersion in water for 96 hours at 85 °C (i.e., the dry T_g and wet T_g). The water uptake and difference between both T_g 's, also called the wet T_g knockdown, are taken as measure for hydrolytic stability.¹⁰³

Most cyanate esters are cured using the following cure protocol: 1 hour at 150 °C, 24 hours at 210 °C with a 5 °C min⁻¹ heating ramp, yielding 'as-cured' resins. Although most as-cured resins reach a complete cure, a post-cure at elevated temperature, up to 350 °C, is frequently added to attain a fully-cured resin. Decomposition of the CERs during this additional post-cure may occur, resulting in fully-cured resin with lower thermomechanical properties than the as-cured resins. This aspect complicates the interpretation of the data and extraction of structure–property relations. Therefore, this review reports the data of as-cured resins if: (i) a complete cure was achieved and (ii) the as-cured resin was fully characterised. All bio-bisphenols, interesting petroleum-based references and their structural relations are presented in Fig. 9. Details and collected data of the uncured and cured cyanate esters are summarized in Tables 6, 7 and represented in Fig. 10.

In 2015 Harvey *et al.*⁵⁶ presented cyanate esters derived from *meta*-methyl alkylated bisphenols: *p,p'*-BPF-3M (17), *p,p'*-BPE-3M (18) and *p,p'*-BPP-3M (19) yielding the following CERs: *p,p'*-BPF-3M-Cy (17), *p,p'*-BPE-3M-Cy (18) and *p,p'*-BPP-3M-Cy (19). All resins, except *p,p'*-BPP-3M-Cy (19) which was liquid at RT, were obtained as white solids with m.p. of 88 °C and 105 °C for *p,p'*-BPF-3M-Cy (17) and *p,p'*-BPE-3M-Cy (18), respectively (Table 6, Fig. 10). A complete cure was achieved in a dynamic DSC scan, showing $T_i \geq 200$ °C, $T_p \geq 245$ °C and

processing windows above 120 °C (Table 6). Unclear complications during cure caused voids in the *p,p'*-BPF-3M-Cy (17) resin limiting its characterisation. All as-cured resins showed similar thermal stability, comparable to the bisphenol reference resins with $T_{d5\%} \geq 410$ °C, $T_{d50\%} > 500$ °C and high char yield at 600 °C above 50% (Table 7). T_g reported for the as-cured resins was 271 °C and 256 °C for *p,p'*-BPE-3M-Cy (18) and *p,p'*-BPP-3M-Cy (19), respectively. This indicated that the alkyl chain elongation lowers the resins T_g (Fig. 10). Furthermore, *p,p'*-BPE-3M-Cy (18) and *p,p'*-BPP-3M-Cy (19) showed a water uptake of 2.11% and 1.84% and wet T_g knockdown of 64 °C and 58 °C, respectively. These values are comparable to the commercial bisphenol references (Table 7), and show that the presence of *meta*-methyl groups, in contrast to *ortho*-methyl groups, does not improve the hydrolytic stability.⁵⁶ Noteworthy, the thermal stability of *m*-methylated *p,p'*-BPE-3M-Cy (18) is slightly higher than the *o*-methylated *p,p'*-BPE-2M-Cy, showing an increase of 10 °C for $T_{d5\%}$ and a 10% higher char yield at 600 °C (Table 7).⁵⁶

Subsequently, Harvey *et al.* (2016)⁵⁰ presented *p,p'*-BPF-3iP-6M-Cy (16), a cyanate ester resin synthesized from a carvacrol based bisphenol, characterised by *ortho*-methyl and *meta*-isopropyl substituents. *p,p'*-BPF-3iP-6M-Cy (16) was obtained as a white solid with 117 °C m.p. A complete cure was achieved upon heating in a dynamic DSC scan, showing T_i of 194 °C, T_p of 275 °C and processing window of 77 °C. The resin showed excellent thermal stability with $T_{d5\%}$ of 390 °C, only 10 °C lower than the commercial bisphenol references and high char yield at 600 °C (i.e. 32%). Besides, at temperatures above 400 °C the reference resins showed significant higher thermal stability (Table 7, Fig. 10). Comparing *p,p'*-BPF-3iP-6M-Cy (16) with *p,p'*-BPE-2M-Cy, showed that the thermal stability at elevated temperature was lowered by the presence of the isopropyl substituents. Interestingly, the resin showed high T_g of 224 °C, a remarkably low water uptake of 0.7% and wet T_g knockdown of only 3 °C. These results showed that, in addition to the beneficial impact of *o*-methyl groups, the hydrolytic stability might be further enhanced by additional hydrophobic substituents, like the isopropyl groups in *meta* position.⁵⁰

In 2013, Meylemans *et al.*¹⁰⁷ presented cyanate ester resins based on bisphenol structures preserving similar alkylation substituents *ortho* to and on the carbon bridge, but characterised by the *m,m'*-isomer orientation and the presence of *o*-methoxy groups. The presented cyanate esters, viz. *m,m'*-BGF-4M-Cy (26), *m,m'*-BGE-4M-Cy (27) and *m,m'*-BGP-4M-Cy (28), were all solid at RT showing m.p. of 125 °C, 91 °C and 120 °C, respectively. The differences in m.p. were attributed to the space group symmetry, thus *m,m'*-BGF-4M-Cy (26) and *m,m'*-BGP-4M-Cy (28) showed to crystallize in the monoclinic space group, whereas *m,m'*-BGE-4M-Cy (27) crystallized in the triclinic space group. Compared to the reported m.p. of their analogous *p,p'*-isomer lacking *o*-methoxy moieties (i.e., *p,p'*-BPF-3M-Cy (17), *p,p'*-BPE-3M-Cy (18) and *p,p'*-BPP-3M-Cy (19), Harvey *et al.* (2015)⁵⁶ showed that the presence of the *o*-methoxy groups and/or the *m,m'*-isomer orientation signifi-

Table 6 Physical properties of uncured cyanate esters and curing reactivity

Ref	Nr.	Bisphenol	Yield ^b [mol%]	Physical properties uncured resin			Curing – reactivity			
				Phase ^c	Colour	T _m [°C]	T _i ^d [°C]	T _p ^d [°C]	H _r ^d [kJ eq. ⁻¹]	Processing window [°C]
Commercial and synthesized cyanate ester resin references										
102	—	<i>p,p'</i> -BPA	—	Solid	White	82	270	330	108	188 ^a
102	—	<i>p,p'</i> -BPE	—	Liquid	White	—	180	260	103	180 ^a
103	—	<i>p,p'</i> -BPE-2M	48 ^a	Solid	White	73	219	327	101	146 ^a
103	—	<i>p,p'</i> -BPA-2M	79 ^a	Solid	White	82	211	315	112	129 ^a
Cyanate ester resins from bio-based bisphenols										
50	16	<i>p,p'</i> -BPF-3iP-6M	91	Solid	White	117	194	275	112	77 ^a
56	17	<i>p,p'</i> -BPF-3M	81	Solid	White	88	210 ^a	245 ^a	109–117	122 ^a
56	18	<i>p,p'</i> -BPE-3M	80	Solid	White	105	225 ^a	300 ^a	109–117	120 ^a
56	19	<i>p,p'</i> -BPP-3M	96	Liquid	White	—	200 ^a	300 ^a	109–117	>180 ^a
54	26	<i>m,m'</i> -BGF-4M	98	Solid	—	125	200	272	88	75
107	26	<i>m,m'</i> -BGF-4M	96	Solid	White	125	146 ^a	216	106	20
107	27	<i>m,m'</i> -BGE-4M	88	Solid	White	91	211 ^a	283	104	120
107	28	<i>m,m'</i> -BGP-4M	46	Solid	White	120	180 ^a	285	99	60
54	29	<i>m,m'</i> -BGF-4E	98	Solid	—	108	223	309	61	115
54	30	<i>m,m'</i> -BGF-4P	97	Solid	—	109	219	309	65	110
107	25	<i>o,o'</i> -BGF-4M	96	Solid	White	151	151 ^a	226	59	0 ^a

^a Data extracted from experimental information, plots or pictures in reference. ^b Theoretical yield. ^c Phase at room temperature (RT). ^d Dynamic DSC scan(s) 10 °C min⁻¹ to determine the onset of cure (T_i), the peak exotherm temperature (T_p), the heat of polymerization (H_r) and processing window.

Table 7 Physical properties and thermal stability of cured cyanate ester resins. curing protocol 1 h–150 °C, 24 h–210 °C ramp 5 °C min⁻¹ for all references except 54 here the data corresponds to resins cured following the protocol 1 h–150 °C, 24 h–210 °C, 4 h–280 °C ramp 5 °C min⁻¹

Ref	Nr.	Bisphenol	Physical properties cured resin						Thermal stability ^e				
			Degree of cure ^b [%]	Cross-link density [mmol cm ⁻³]	Density [g cm ⁻³]	T _g ^c [°C]	Water uptake [wt%]	Wet T _g [°C]	T _{d5%} [°C]	T _{d10%} [°C]	T _{d50%} [°C]	T _{dmax} [°C]	Char _{600°C} [%]
Commercial and synthesized cyanate ester resin references													
102	—	<i>p,p'</i> -BPA	—	2.9	1.21	275	1.34	240	402 ^a	412 ^a	555 ^a	—	48 ^a
102	—	<i>p,p'</i> -BPE	—	3.1	1.23	291	1.75	239	402 ^a	412 ^a	>600 ^a	—	55 ^a
103	—	<i>p,p'</i> -BPE-2M	99	—	1.14	246 ^d	1.21	240	401	405 ^a	560 ^a	405	48
103	—	<i>p,p'</i> -BPA-2M	98	—	1.16	247 ^d	1.05	222	401	405 ^a	500 ^a	405	43
Cyanate ester resins from bio-based bisphenols													
50	16	<i>p,p'</i> -BPF-3iP-6M	Complete	—	1.06	224 ^d	0.70	221	390	400 ^a	427 ^a	—	32 ^a
56	17	<i>p,p'</i> -BPF-3M	Complete	—	—	—	—	—	410 ^a	420 ^a	>500 ^a	—	59 ^e
56	18	<i>p,p'</i> -BPE-3M	Complete	—	1.19	271	2.11	207	412 ^a	420 ^a	>500 ^a	—	57 ^e
56	19	<i>p,p'</i> -BPP-3M	Complete	—	1.16	256	1.84	198	412 ^a	422 ^a	>500 ^a	—	52 ^e
54	26	<i>m,m'</i> -BGF-4M	Complete	—	—	231	1.75	—	375	383	404 ^a	396	34 ^a
107	26	<i>m,m'</i> -BGF-4M	Complete	2.6	1.22	257	2.05	193	360	366	380 ^a	—	35
107	27	<i>m,m'</i> -BGE-4M	Complete	2.4	1.20	257	2.61	185	330	344	375 ^a	—	28
107	28	<i>m,m'</i> -BGP-4M	Complete	2.3	1.19	257	3.21	161	329	345	380 ^a	—	27
54	29	<i>m,m'</i> -BGF-4E	Complete	—	—	231	1.36	—	389	392	407 ^a	401	33 ^a
54	30	<i>m,m'</i> -BGF-4P	Complete	—	—	193	1.18	—	389	393	415 ^a	411	27 ^a
107	25	<i>o,o'</i> -BGF-4M	<60	2.6	1.24	181	2.05	—	317	326	370 ^a	—	33

^a Data extracted from experimental information, plots or pictures in reference. ^b Degree of cure defined by author after curing protocol -not after dynamic DSC scan-. ^c DMA experiments were used to determine the glass transition temperature (T_g) defined by the maximum of $\tan(\delta)$ or for ^d the peak of the loss modulus. ^e Thermal degradation determined by TGA under nitrogen atmosphere.

ent next to the carbon bridge. *m,m'*-BGF-4M-Cy (26), *m,m'*-BGF-4E-Cy (29) and *m,m'*-BGF-4P-Cy (30) were obtained as solid resins with m.p. of 125 °C, 108 °C and 109 °C, respectively. In a dynamic DSC scan the resins did not reach complete cure. In general, the chain elongation broadens the processing window but slows down the cure of the resin. Therefore, the authors added a post cure of 4 hours at 280 °C to the curing

protocol to achieve fully cured, void free resin pucks.⁵⁴ Noteworthy, the processing window observed by Meylemans *et al.* (2013)¹⁰⁷ for *m,m'*-BGF-4M-Cy (26) was much smaller than the one reported by Koelewijn *et al.* (2017).⁵⁴ This confirms that the presence of trace impurities significantly affects the curing reaction.¹⁰⁴ T_g of *m,m'*-BGF-4M-Cy (26) and *m,m'*-BGF-4E-Cy (29) is equal to 231 °C and lowered upon further

Fig. 10 Polymer properties of the bio-based and reference cyanate ester resins. Representation of (A) the onset thermal degradation temperature, 5% weight loss temperature ($T_{d5\%}$) of the cured CERs under nitrogen atmosphere (B) the glass transition temperature (T_g) of the cured CERs (C) the melt temperature (T_m) of the uncured CERs and (D) the water uptake in wt% of the cured CERs after immersion in water 96 h at 85 °C.

elongation of the 4-alkyl chain, showing T_g of 193 °C for m,m' -BGF-4P-Cy (30) (Fig. 10). Moreover, the water uptake is lowered with alkyl chain elongation, showing a water uptake of 1.75%, 1.36% and 1.18% for m,m' -BGF-4M-Cy (26), m,m' -BGF-4E-Cy (29) and m,m' -BGF-4P-Cy (30), respectively. This indicated that the hydrophobicity of the 4-alkyl chains had a favourable impact on the hydrophobicity of the final thermosetting polymer. The thermal stability was similar for all resins, showing $T_{d5\%} \geq 375$ °C, $T_{d50\%} \geq 404$ °C and char yield $\geq 27\%$. In contrast to all other reported CERs, a similar char yield at 600 °C was observed under nitrogen and air atmosphere.⁵⁴

Careful comparison of m,m' -BGP-4M-Cy (28) and m,m' -BGF-4P-Cy (30), highlights the importance of the alkyl chain position to beneficially influence water uptake. For the alkyl chain next to the carbon bridge, the water uptake decreases

with elongation, for an alkyl chain on the carbon bridge, the water uptake increases with elongation.

Finally, the cyanate ester of an o,o' -isomer is reported by Meylemans *et al.* (2013).¹⁰⁷ o,o' -BGF-4M-Cy (25) is obtained as a solid with m.p. of 151 °C. Hence, the o,o' -isomer orientation increased the m.p. of the resin with 26 °C compared to the analogous m,m' -isomer, m,m' -BGF-4M-Cy (26). The cure onset immediately followed the resin melt in a dynamic DSC scan and an incomplete cure was achieved. Hence, a post cure of 4 hours at 250 °C was added to achieve a complete cured resin puck, reaching a dry T_g of 238 °C.¹⁰⁷ Unfortunately all other parameters like water uptake, wet T_g and thermal stability were not reported for this fully-cured resin. To avoid any confusion, the reported data for the as-cured (*i.e.* incomplete cured) resin will not be further discussed, but it is shown in Table 7.

In general, m.p. of the cyanate esters is influenced by (i) the isomer orientation and (ii) the presence of *o*-methoxy groups. T_g of CERs is lowered upon elongation of the 4-alkyl chain on the bisphenol. Furthermore, the thermoset's thermal stability decreased by the presence of *o*-methoxy moieties. Whereas the presence of *o*-methoxy groups increased the CERs water uptake, the presence of *o*-methyl decreased the CERs water uptake. Moreover, the introduction of hydrophobic alkyl chains *ortho* to the carbon bridge significantly lowered water uptake. Combining both favourable structural features, the *p,p'*-BPF-3iP-6M-Cy (**16**) showed the highest hydrolytic stability with a low water uptake of only 0.7% and wet T_g knockdown of only 3 °C. To conclude, the current bio-based CERs show T_g 's ranging from 193 °C to 271 °C and thermal stability with $T_{d5\%} \geq 329$ °C, $T_{d50\%} \geq 375$ °C and char yield $\geq 27\%$, and thus reaching the performance of the fossil-based bisphenol CERs. Moreover, through the use of bio-bisphenols characterized by hydrophobic alkyl chains *ortho* to the carbon bridge, hydrolytically stable CERs were obtained surpassing the stability of the current bisphenol references.

3.5 Benzoxazine resins

The formation of heterocyclic compounds as benzoxazine resins (Bzs), through the Mannich reaction of phenols, primary amines and formaldehyde is known since 1944. In an attempt to improve the material functionality, Ning X. and Ishida H. presented the first bifunctional benzoxazine resin (Bz) from *p,p'*-BPA, methylamine and formaldehyde in 1994.¹⁰⁸ Nowadays, BPA is still an important precursor for the synthesis

of benzoxazines (Fig. S2e, ESI†).¹⁰⁹ The benzoxazines cure upon heating by a ring-opening polymerization reaction yielding a polybenzoxazine network (PBz). Usage of bifunctional monomers results in a cross-linked network. This polymerization is initiated by phenols with a free *ortho*-position, *in situ* added or produced by self-dissociation of the Bz monomer upon heating. In addition, the polymerization reaction can be accelerated by the addition of a Lewis acid catalyst.¹⁰⁸ During the last two decades, the synthesis of diverse PBz attracted great interest as they combine the thermal flame retardant of phenolic resins and the design flexibility of epoxy resins.¹¹⁰ Showing a low water adsorption, low flammability, zero volume shrinkage upon curing, low dielectric constant and high T_g , PBz are used in diverse applications, such as aerospace materials and anticorrosive coatings.^{109,110} All Bz monomers synthesized from bio-bisphenols, related petroleum-based references and their structural relations are presented in Fig. 11. Details and collected data of the uncured and cured Bzs are summarized in Tables 8, 9 and represented in Fig. 12.

In 2016, Periyasamy *et al.*⁶² presented the Bz monomer derived from *mix'*-BGF, isomer distribution not mentioned by author, using stearylamine, yielding *mix'*-BGF-SBz (**2-21-22**). In this abbreviation 'SBz' stands for a stearylamine (S) based benzoxazine monomer (Bz). This monomer was obtained as a solid at RT, showing m.p. of 94 °C. The BPF reference SBz, *mix'*-BPF-SBz was recently reported by Manoj *et al.* (2020)¹⁰⁹ and showed to be liquid at RT.¹⁰⁹ This implies that the presence of (i) the *o*-methoxy groups and/or (ii) other isomer orientations increased m.p. of the Bz monomer. Upon heating in a

Fig. 11 Benzoxazine resins of bio-bisphenols and reference bisphenols. The representation of so far reported benzoxazines synthesized from bio-bisphenols, in addition to the petroleum-based references, and their structural relations.

Table 8 Physical properties of uncured benzoxazine resins and curing reactivity

Ref.	Nr.	Bisphenol	Yield ^b [mol%]	Physical properties uncured resin			Curing – reactivity			
				Phase ^c	Colour	T _m [°C]	T _i ^d [°C]	T _p ^d [°C]	H _r ^d [kJ eq. ⁻¹]	Processing window [°C]
Reagent: stearylamine										
109	—	<i>mix'</i> -BPF	—	—	—	—	209	239	—	>189 ^a
62	2–21–22	<i>mix'</i> -BGF	89	Solid	Pale-yellow	94	216	238	—	122
Reagent: furfurylamine										
112	—	<i>p,p'</i> -BPA	57	Solid	—	105	233	245 ^a	266 ^a	142
62	2–21–22	<i>mix'</i> -BGF	91	Solid	Pale-yellow	117	194	224	—	77
51	11	<i>p,p'</i> -BGF _{UR}	76	Solid	White	126; 153	204	242	204 ^a	51
113	5	<i>p,p'</i> -DPA	86	Solid	Brown-yellow	—	150	185	—	—
Reagent: 1,3,5-triphenylhexahydro,1,3,5-triazine										
114	—	<i>p,p'</i> -BPA	—	—	—	—	210	256	—	—
113	—	<i>p,p'</i> -BPA	—	—	—	—	223	234	—	—
114	5	<i>p,p'</i> -DPA	95	Solid	Yellowish	—	150	192	—	—
47	5	<i>p,p'</i> -DPA	95	Solid	Yellowish	—	152	189	311 ^a	—
114	6	<i>p,p'</i> -DPA-Me	93	Solid	Pale-yellow	—	210	261	—	—
47	6	<i>p,p'</i> -DPA-Me	92	Solid	Yellowish	—	167	231	331 ^a	—

^a Data extracted from experimental information, plots or pictures in reference. ^b Theoretical yield. ^c Phase at room temperature (RT). ^d Dynamic DSC scan(s) 10 °C min⁻¹ to determine the onset of cure (T_i), the peak exotherm temperature (T_p), the heat of polymerization (H_r) and processing window.

Table 9 Physical properties and thermal stability of cured benzoxazine resins

				Thermal stability ^d						
Ref.	Nr.	Bisphenol	Cure protocol	T _g ^b [°C]	LOI ^c	T _{d5%} [°C]	T _{d10%} [°C]	T _{d50%} [°C]	T _{dmax} [°C]	Char _{800°C} ^d [%]
Reagent: stearylamine										
109	—	<i>mix'</i> -BPF	5 h–250 °C	—	29.1	391	414	530 ^a	461	29 ^a
62	2–21–22	<i>mix'</i> -BGF	1 h–100 °C; 150 °C, 200 °C, 250 °C	124	32.8	349	381	525 ^a	—	38
Reagent: furfurylamine										
112	—	<i>p,p'</i> -BPA	1 h–160 °C; 2 h–200 °C, 2 h–240 °C	308	36.7	347	391	750 ^a	—	48 ^a
62	2–21–22	<i>mix'</i> -BGF	1 h–100 °C; 150 °C, 200 °C, 250 °C	147	38.5	382	417	>800	—	52
51	11	<i>p,p'</i> -BGF _{UR}	1 h–140 °C; 160 °C, 180 °C, 200 °C, 220 °C, 240 °C	290	42.3	340	375	>800 ^a	—	62
113	5	<i>p,p'</i> -DPA	1 h–140 °C; 170 °C, 190 °C, 210 °C, 240 °C	—	37.6 ^a	340	380 ^a	800 ^a	449	50
Reagent: 1,3,5-triphenylhexahydro,1,3,5-triazine										
114	—	<i>p,p'</i> -BPA	2 h–140 °C; 215 °C, 235 °C, 260 °C	172	31.1 ^a	310 ^a	366	490 ^a	427	34
113	—	<i>p,p'</i> -BPA	1 h–210 °C; 2 h–220 °C; 230 °C, 1 h–240 °C	—	29.7 ^a	331	380 ^a	470 ^a	406	31
114	5	<i>p,p'</i> -DPA	2 h–140 °C; 160 °C, 180 °C, 190 °C	206	30.3 ^a	310 ^a	348	450 ^a	425	32
47	5	<i>p,p'</i> -DPA	1 h–140 °C; 160 °C, 180 °C, 200 °C, 220 °C, 240 °C	—	32.7	344	377	501	442	38
114	6	<i>p,p'</i> -DPA-Me	2 h–140 °C; 215 °C, 235 °C, 260 °C	270	29.9 ^a	360 ^a	379	450 ^a	420	31
47	6	<i>p,p'</i> -DPA-Me	1 h–140 °C; 160 °C, 180 °C, 200 °C, 220 °C, 240 °C	—	30.5	335	361	479	448	33

^a Data extracted from experimental information, plots or pictures in reference. ^b DMA experiments were used to determine the glass transition temperature (T_g) defined by the maximum of tan(δ). ^c LOI following the Van Krevelen and Hoftzyer relation. ^d Thermal degradation determined by TGA under nitrogen atmosphere.

dynamic DSC scan, *mix'*-BGF·SBz (**2-21-22**) and *mix'*-BPF·SBz show similar T_i and T_p of the cure reactions, resulting in wide processing windows of 122 °C and >189 °C for the resins, respectively (Table 8). Surprisingly, this indicates that, despite the occupied *ortho*-position, the presence of the *o*-methoxy groups does not influence the reactivity for the ring-opening polymerization. T_g of the *mix'*-BGF·SBz (**2-21-22**) thermoset was found 124 °C. Although T_{d5%} 42 °C lower than the *mix'*-BPF·SBz thermoset reference, the *mix'*-BGF·SBz (**2-21-22**) thermoset showed similar T_{d50%} and even a 9% higher char yield at 800 °C. This resulted in a higher limiting oxygen index (LOI) for the *mix'*-BGF·SBz (**2-21-22**) thermoset (cfr. *mix'*-BPF·SBz

thermoset), derived by the Van Krevelen and Hoftzyer relation between char yield and the LOI index (Table 9).^{62,111}

The introduction of furanic groups in Bz monomers showed to enhance T_g, storage moduli and thermal stability of the cured resin. This is mostly attributed to the active role of the furanic groups during the ring-opening polymerization, yielding di-substituted furanic groups and highly cross-linked resins. In addition, the presence of furanic groups in the resins network enhances hydrogen bond formation limiting molecular mobility in the cured network, increasing T_g.¹¹² In this regard, Periyasamy *et al.* (2016)⁶² and Yang *et al.* (2020)⁵¹ presented the Bzs of the bisguaiacols *mix'*-BGF (**2-21-22**) and

p,p'-BGF_{UR} (**11**) and furfurylamine yielding *mix'*-BGF-FBz (**2-21-22**) and *p,p'*-BGF_{UR}-FBz (**11**), respectively. Both Bzs were obtained as solids, with m.p. of 117 °C for *mix'*-BGF-FBz (**2-21-22**) and two observed melting points of 126 °C and 153 °C for *p,p'*-BGF_{UR}-FBz (**11**). T_i of both resins was around 200 °C in a dynamic DSC scan, but T_p was found 18 °C lower for *mix'*-BGF-FBz (**2-21-22**), indicating slightly lower reactivity of the *p,p'*-BGF_{UR}-FBz (**11**). In addition, a lower cure enthalpy was observed for *p,p'*-BGF_{UR}-FBz (**11**) (204 kJ eq.⁻¹) compared to the commercial BPA-based Bz, *p,p'*-BPA-FBz (266 kJ eq.⁻¹).¹¹² According to Yang *et al.*(2020)⁵¹ this showed that the polymerization reaction of *p,p'*-BGF_{UR}-FBz (**11**) was impeded by the presence of *ortho*-methoxy groups, occupying one of the favourable substitution positions for the ring-opening polymerization.⁵¹ For the *mix'*-BGF-FBz (**2-21-22**) thermoset T_g of 147 °C was observed. This is more than 150 °C lower than the commercial *p,p'*-BPA-FBz thermoset, showing the impact of the *o*-methoxy groups and/or the methylene bridge on T_g , *i.e.*, providing a higher rotational degree to the resin's network. The former aspect was tackled by incorporation of an additional furan on the bisguaiacol carbon bridge showing T_g of 290 °C for the *p,p'*-BGF_{UR}-FBz (**11**) thermoset (Table 9, Fig. 12). Moreover, it was shown by Yang *et al.*(2020)⁵¹ that at elevated temperatures, residual furanic groups further polymerize yielding an (even) higher cross-linked resin. This feature has a beneficial impact on the thermoset's thermal stability, showing a char yield at 800 °C of 62% and LOI of 42.3.⁵¹ Noteworthy, the *mix'*-BGF-FBz (**2-21-22**) thermoset showed excellent thermal stability too, with $T_{d5\%}$ of 382 °C, $T_{d50\%}$ above 800 °C, char yield at 800 °C of 52% and LOI of 38.5.⁶² This shows that bio-based PBzs are reaching and/or surpassing the thermal stability of the conventional BPA-based PBz, showing $T_{d5\%}$ of 347 °C, $T_{d50\%}$ of 750 °C, char yield at 800 °C of 48% and LOI of 36.7 (Table 9).

In addition, Zhan *et al.* (2020)¹¹³ presented the Bz monomer derived from *p,p'*-DPA (**5**) and furfurylamine, *p,p'*-DPA-FBz (**5**). Interestingly, the T_i was found more than 80 °C lower than *p,p'*-BPA-FBz (Table 8). This was attributed to the presence of the carboxyl group, which is able to catalyse the ring-opening polymerization reaction, hence, lower the cure onset temperature (T_i). Moreover, the thermal stability of the *p,p'*-DPA-FBz (**5**) thermoset, with $T_{d5\%}$ of 340 °C, $T_{d50\%}$ of 800 °C, char yield at 800 °C of 50% and LOI of 37.6, was comparable to the BPA reference.¹¹³

Looking into the potential of *p,p'*-DPA and *p,p'*-DPA-esters, like *p,p'*-DPA-Me (**6**), Zúñiga *et al.* (2011)¹¹⁴ and Yan *et al.* (2016)⁴⁷ synthesized *p,p'*-DPA-ABz (**5**) and *p,p'*-DPA-Me-ABz (**6**) using 1,3,5-triphenylhexahydro-1,3,5-triazine as amine precursor. These Bz monomers are characterised by the presence of aryl structures that can participate in the polymerization reaction. Comparing the exotherm cure events of *p,p'*-DPA-ABz (**5**) and *p,p'*-DPA-Me-ABz (**6**) in a dynamic DSC scan, both authors observed a lower T_i for *p,p'*-DPA-ABz (**5**) around 150 °C, attributed to the presence of carboxylic groups (Table 8). The cure exotherm of *p,p'*-DPA-Me-ABz (**6**) was comparable to the BPA reference, *p,p'*-BPA-ABz. Moreover, it was shown that, in

addition to the ring-opening polymerization, esterification or transesterification of the acidic groups and the free hydroxyl groups (*i.e.*, phenolic OH formed during ring opening of oxazines) in *p,p'*-DPA-ABz (**5**) and *p,p'*-DPA-Me-ABz (**6**) increased the cross-link density in the cured network. The thermosets showed T_g of 206 °C and 270 °C for *p,p'*-DPA-ABz (**5**) and *p,p'*-DPA-Me-ABz (**6**), respectively, surpassing that of the reference *p,p'*-BPA-ABz (172 °C). With $T_{d5\%} \geq 310$ °C, $T_{d50\%} \geq 450$ °C, char yield at 800 °C $\geq 31\%$ and LOI above 30, the thermal stability of thermosets showed to be comparable to the reference *p,p'*-BPA-ABz thermosets, showing $T_{d5\%} \geq 310$ °C, $T_{d50\%} \geq 470$ °C, char yield at 800 °C above $\geq 31\%$ and LOI above 30.¹¹⁴

In general, it is shown that (i) the bisphenol isomer orientation and/or (ii) the presence of *o*-methoxy groups influenced the Bz monomer melting point. T_g of the thermoset is lowered by the presence of *o*-methoxy moieties but increased through the incorporation of a furanic group on the carbon bridge, impacting the polymer rigidity and reaching a higher cross-link density. A T_g surpassing the BPA reference PBz, was found for the PBz of *p,p'*-DPA (**5**) and *p,p'*-DPA-Me (**6**) with T_g of 206 °C and 270 °C, respectively. This was attributed to the acidic group on the carbon bridge, increasing the cross-link density through esterification and transesterification reactions with the free hydroxyl groups formed during the conventional ring-opening polymerization of the oxazines. Moreover, the presence of free carboxyl groups showed to catalyse the curing reaction, resulting in a lower cure onset temperature. In addition, the thermal stability and LOI of all bio-based PBz was found comparable or even higher than the BPA-references, highlighting the potential of bio-based bisphenols for the synthesis of high-performance benzoxazine resins.

4. *In vitro* oestrogenic activity: structure–toxicity

The adverse health effects (*e.g.*, cancer,^{11,12} reproductive issues,^{13,14} obesity¹⁵) linked to human BPA exposure originate from its ability to interfere with the endocrine system. In this regard, BPA is recognized as a synthetic xenoestrogen; a synthetic chemical structure that can mimic the natural oestrogen hormones, such as 17 β -oestradiol (E2).¹¹⁵ Moreover, a metabolite of BPA, *viz.* 4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene (MBP), showed a 1000-fold higher oestrogenic activity (EA) compared to BPA.¹¹⁶ Hence, the pharmacophore of E2 provides valuable information to understand how BPA as well as its metabolites interact with the oestrogen receptors α (ER α) and/or β (ER β) and how EA can be designed out of the next generation of BPA molecules.¹¹⁷ In general, the pharmacophore of E2 is described as two hydroxyl groups separated by a hydrophobic spacer which includes an aromatic ring. Fig. 13 presents the molecular structures of E2, BPA and MBP. Overall, the key feature for oestrogen receptor binding affinity is the hydroxyl group on the aromatic A-ring (*i.e.*, 3-OH) which binds with the receptor *via* hydrogen bonding (*i.e.*, H-bond donor or acceptor).¹¹⁸ Therefore, additional substituents on the A-ring

Fig. 12 Curing and polymer properties of the benzoxazine resins. Representation of (A) the onset thermal degradation temperature, 5% weight loss temperature ($T_{d5\%}$) of the cured Bzs under nitrogen atmosphere (B) the glass transition temperature (T_g) of the cured Bzs (C) the cure peak temperature (T_p) determined during a dynamic DSC scan, heating ramp $10\text{ }^{\circ}\text{C min}^{-1}$ and (D) the LOI index of the cured Bzs. The benzoxazines are divided in sections according to the amine reagent used from left to right: stearylamine, furfurylamine and 1,3,5-triphenylhexahydro,1,3,5,-triazine.

impact the EA either by (i) altering the acidity of the phenolic 3-OH, (ii) competitive intramolecular H-bonding sites and/or (iii) steric interference. In addition, some other structural alterations to E2's molecular structure are not well tolerated and significantly lower the EA binding affinity: (i) substituents incorporated at position 6 and/or (ii) polar substituents incorporated at position 11 (Fig. 13).¹¹⁸

In general, the molecular structures of the presented bio-based bisphenols (Fig. 1) differ in four structural aspects: (i) isomer orientation, (ii) aromatic *o*-substituents (*i.e.*, hydroxyl, methyl, methoxy), (iii) carbon bridge substituents, and (iv) aromatic *m*- or *p*-substituents (*i.e.*, alkyl).

Hence, to avoid the synthesis of regrettable BPA alternatives, the impact of these four structural features on the

bisphenol's EA will be discussed in this section. More specifically, the following results and trends were shown by *in vitro* oestrogen receptor transactivation or binding assays providing a reliable assessment of the compounds oestrogen activity, expressed as potency and efficacy (*vide infra*) or binding affinity (RBA) for ER α and/or ER β . However, to assess the integral endocrine disruptive character of the compounds additional *in vitro* assays evaluating the affinity for other receptors belonging to the steroid/thyroid nuclear hormone receptor superfamily should be performed as well, followed by *in vivo* screenings, evaluating the compound's and its metabolites EA in living organisms.^{17,119}

Moreover, computational modelling (*i.e.*, *in silico*) is an emerging method to predict compounds' toxicity. Herein,

Fig. 13 Molecular structure of 17 β -oestradiol, BPA and MBP. Representation of the molecular structure of (A) 17 β -Oestradiol (E2), (B) *p,p'*-BPA and (C) MBP. In addition, an overview of structural modifications (in)tolerated by the α -oestrogen receptor (ER- α) based on ref. Anstead *et al.* (1997).¹¹⁸

molecular docking software is used to compute the nuclear receptor binding affinity for multiple nuclear receptors (*e.g.*, the oestrogenic receptor ER α).¹²⁰ When correlated to experimental toxicity data (*e.g.*, results of *in vitro* and/or *in vivo* experiments) a powerful predictive tool might be developed.^{121,122} Being time, labour and money efficient, it is believed that *in silico* screenings will become an important predictive feature in future bisphenol design, in particular helpful in preliminary screenings.¹²³ However, there are still disadvantages (*e.g.*, insufficient data, complex mechanism)¹²³ impacting the accuracy of *in silico* results and the structure-toxicity relationships derived thereof.¹²¹ Hence, while recognizing the importance and complementary value of *in silico*, *in vitro* and *in vivo* data, only *in vitro* assays are discussed in this study.

Screening of the EA by *in vitro* oestrogen receptor transactivation assays induces a dose-dependent signal upon interaction of a compound with the oestrogen receptor at varying concentrations. Literature data are discussed in terms of potency and efficacy. Potency is mostly expressed by the half-maximal effective concentration (EC₅₀). Accordingly, the higher the EC₅₀, the lower the potency of the compound. Efficacy is the maximum effect induced for a given compound, and mostly expressed as $E_{\max}$ relative to the E2 reference. For *in vitro* oestrogen receptor binding assays, the potency is typically expressed by the half-maximal inhibitory concentration (IC₅₀), *i.e.*, the concentration required to displace 50% of a bound radioligand. This is, mostly, expressed relative to the IC₅₀ concentration of E2 and defined as the relative binding affinity (RBA).

4.1 Isomer orientations

In 2003, Coleman *et al.*¹²⁴ showed a two-fold lower potency for *o,p'*-BPA compared to *p,p'*-BPA.¹²⁴ At a test concentration of

5 μ M (in terms of efficacy) Szafran *et al.* (2017)¹²⁵ found $E_{\max}$ values, of 57% and 19% for *p,p'*- and *o,o'*-BPA isomers (relative to E2 = 100%), respectively.¹²⁵ Although differences are modest, these results clearly show that bisphenol isomer orientation impacts EA. In this regard, Koelewijn *et al.* (2019)⁵⁹ screened the EA of the bio-based *p,p'*- (2) and *m,p'*-BGF (22) isomers over a broad concentration range (up to the solubility limit, >100 μ M). In this way, a partial dose-response curve was obtained starting at 10 μ M, allowing statistical comparison in terms of potency and efficacy. A *quasi*-similar potency was reported for the *p,p'*- and *m,p'*-isomer, but the latter isomer showed a lower efficacy. This confirms that deviations from the ideal *para*-oriented position of the aromatic hydroxyl group lowers the EA of bio-based bisphenols; a trend also observed in common bisphenols and E2.⁵⁹

4.2 *ortho*-substituents

The influence of *o*-hydroxy, *o*-methyl or *o*-methoxy A-ring substituents on the ER binding affinity of E2 was examined by Zhu *et al.* (2006).¹²⁶ In terms of potency, both receptors (*i.e.*, ER α and ER β) revealed a similar trend of decreasing binding affinity: *o*-hydroxy > *o*-methyl > *o*-methoxy. In particular, the RBAs were shown to be 70%, 9% and 2% for ER α and 56%, 35% and 1% for ER β .¹²⁶ For BPA, Kitamura *et al.* (2005)¹²⁷ showed a lower EA (in terms of potency) for the one *o*-hydroxylated BPA (*p,p'*-PCA) compared to the tetra-*o*-methylated BPA (*p,p'*-BPA-2,6M) and *p,p'*-BPA showing EC₅₀ values of 1.8 μ M, 0.73 μ M and 0.63 μ M, respectively.¹²⁷ Furthermore, it was shown by Coleman *et al.* (2003)¹²⁴ that unencumbered *para*-phenols showed the highest EA (in terms of potency). A decrease in EA was reported for *p,p'*-BPA-2,6M, indicating that two methyl groups adjacent to the hydroxyl reduce EA.¹²⁴ This was confirmed by Szafran *et al.* (2017)¹²⁵ investigating the

efficacy (at 5 μM) for tetra-*o*-methylated *p,p'*-BPF (*p,p'*-BPF-2,6M) and *o*-methoxylated *p,p'*-BPF (*p,p'*-BGF (2)), observing little to no EA. E_{max} values of 2.3% and -0.6% were reported for *p,p'*-BPF-2,6M and *p,p'*-BGF (2), respectively, compared to 57% for *p,p'*-BPA.¹²⁵ To further investigate the beneficial effect of the *o*-methoxy moieties inhibiting EA in *p,p'*-BGF (2), Koelewijn *et al.* (2019)⁵⁹ determined the EA at concentrations up to 100 μM of *p,p'*-BGF versus *p,p'*-BPF in the same *in vitro* assay, thereby preserving identical molecular structure except for the *o*-methoxy moieties. It was shown that the additional *o*-methoxy groups caused a significant drop in EA, reducing the potency with approximately two orders of magnitude and the efficacy with more than 50%.⁵⁹ More recently, the influence of *o*-methoxy groups on EA was also investigated by Peng *et al.* (2021).¹²⁸ Although the compounds were only screened up to 1 μM , the authors reported a lower efficacy for *p,p'*-BSF (4) compared to *p,p'*-GSF (3).¹²⁸

4.3 Carbon bridge substituents

It has been shown that introducing more hydrophobic substituents (*e.g.*, alkyl chains) on the carbon bridge enhances the EA of bisphenols.^{124,127} Similarly, the EA of bisphenols can be lowered by introducing more polar substituents on the carbon bridge. This was shown by Kitamura *et al.* (2005)¹²⁷ reporting a lower EA for bisphenols with hydrophilic substituents on the carbon bridge (*i.e.*, carboxylic acid, hydroxyl groups).¹²⁷ For example, the bio-based bisphenol, *p,p'*-DPA (5), showed a 10-fold lower RBA compared to *p,p'*-BPA.¹²⁹

4.4 meta-, para- aromatic substituents

In 2006, Zhu *et al.*¹²⁶ showed that the incorporation of a methyl group *meta* to the hydroxyl group of the A-ring in E2 (*i.e.*, position 1), decreased the binding affinity with ER α and ER β by about 90%.¹²⁶ In 2017, Koelewijn *et al.*⁵⁴ examined the EA of *p,p'*-BGF-5M, for which careful comparison with *p,p'*-BGF⁵⁹ did not show a further decrease in EA by the *meta*-methyl substituents. Looking into the EA of the *m,m'*-BGF molecules characterised by *para*-alkyl substituents, a strong reduction in EA was observed with elongation of the 4-alkyl chain. This is reported by a two-fold lower efficacy and 10–100 times lower potency for *m,m'*-BGF-4E (29) and *m,m'*-BGF-4P (30) compared to *p,p'*-BPA.⁵⁴ The same trend was recognized for *m,m'*-BSF-4M (31) and *m,m'*-BSF-4P (32). Both bio-based bisphenols show, respectively, a 19–45 times lower potency and 45%–36% lower efficacy than *p,p'*-BPA.⁵⁵

Hence, it has been shown that some structural features characterising the bio-derived, more particular lignin-derived, phenols (*e.g.*, *o*-methoxy groups, 4-alkyl chain) lower the oestrogenic activity of the resulting bisphenols significantly. Furthermore, the use of carbonyl reagents with more hydrophilic functional groups might further lower the bio-bisphenol oestrogenic activity.

5. Conclusion

During the last decades, extensive research concerning the valorisation of biomass led to a plethora of renewable chemical intermediates, like phenols, aldehydes and ketones, which are interesting alternative substrates for bisphenol chemistry. Accordingly, this innovation transitioned the focus from DPA and DPA-esters to the syntheses of new, more diverse bisphenol structures. In general, the existing bio-bisphenol platform contains 32 bisphenol structures varying in: (i) isomer orientation, (ii) aromatic *o*-substituents (*i.e.*, hydroxyl, methyl, methoxy), (iii) carbon bridge substituents, and (iv) aromatic *m*- or *p*-substituents (*i.e.*, alkyl). Assessing the impact of these four structural features on polymer performance and oestrogenic activity, it was shown that:

Bio-bisphenols made from lignin-derived phenols led to new *m,m'*- and *m,p'*-isomer orientations as well as conventional *o,o'*, *o,p'* and *p,p'*-isomer orientations. *m,p'*-Isomers are as reactive and functional as *p,p'*-isomers, yielding polymers with similar polymer properties. However, the bio-bisphenol isomer orientation clearly influences the melting point, viscosity and cross-link density of corresponding epoxy and cyanate ester resins, thereby impacting the processability and thermomechanical properties of the thermosets. For the different bisphenol isomer orientations, it was shown that the oestrogenic activity of *o,p'*-, *o,o'*- and *m,p'*-isomers is lower compared to the *p,p'*-isomers.

The ***o*-substituents** in bio-bisphenols not only strikingly affected the polymer properties but also the oestrogenic activity. When *o*-hydroxylated bisphenols (*i.e.*, catechol-based) were used to synthesize epoxy resins, a benzodioxane diepoxide by-product was acquired in addition to the tetraepoxide. The benzodioxane by-product includes a free hydroxyl group, catalysing the amine-epoxide curing reaction. Thus, even with high concentrations of this by-product, highly cross-linked epoxy resins with excellent thermomechanical properties were obtained. Use of *o*-methylated bisphenols (*i.e.*, *o*-cresol based) showed enhancement of the hydrolytic stability of cyanate ester resins, significantly lowering the water uptake and constraining the wet T_g knockdown. In general, *o*-methoxy moieties in the DPM core structure (*i.e.*, guaiacol-, syringol-based), moderately, lowered the polymers T_g and thermal stability and increased the resins melting point. For the epoxy resins a beneficial impact on the storage modulus was reported and attributed to hydrogen bonding interactions. Regarding the endocrine disrupting character, a free hydroxyl group was reported as the key structural feature for oestrogenic activity. Hence, *o*-substituents and, moreover, *o*-substituents which induce intramolecular hydrogen bonding, showed to significantly decrease the bisphenol's oestrogenic activity. The most remarkable impact was shown for *o*-methoxylated bisphenols, typical phenolics derived from lignin. Additional *o*-methoxy groups cause a serious drop in the oestrogenic activity, reducing the potency by about two orders of magnitude and the efficacy with more than 50%.

Embedding steric, aromatic and/or polar **substituents on the carbon bridge** showed an efficient way to enhance the ther-

momechanical polymer properties, however, the impact differs for each polymer type. In general, imparting rigidity (e.g., the isopropylidene bridge), intermolecular hydrogen bonding (e.g., free hydroxyl groups) and reactive functional groups (e.g., furan groups, carboxyl groups) increased the polymer's glass transition temperature, storage modulus and thermal stability. For the benzoxazine resins, bio-based thermosets could even surpass the fossil-based thermoset references, showing higher T_g 's and thermal stability. Concerning oestrogenic activity, it was shown that hydrophobic substituents increase the bisphenol oestrogenic activity. Hence, the incorporation of more polar, hydrophilic substituents on the carbon bridge is most preferred in light of lowering the oestrogenic activity.

Adding *para*-alkyl (i.e., 4-alkyl) moieties to the DPM core structure, a typical structure moiety of phenolics derived from lignin, seemed to lower the bisphenol's melting point, as well as the tendency to crystallize in polycarbonates, upon elongation of the 4-alkyl chain. Although moderately lowering the thermal stability, the incorporation of alkyl groups increased the overall hydrophobicity of the resins, enhancing the hydrolytic stability of cyanate ester resins. Moreover, it was shown that the oestrogenic activity decreased upon elongation of the 4-alkyl chains.

Noteworthy, while compiling this systematic review, it was found that the main factor impeding the extraction of clear structure–property and structure–toxicity relationships until now, has been the lack of a consistent analysis, parameter definition and reporting. To provide more qualitative relationships and create more insight for future rational bio-bisphenol design, it is encouraged to include the following in future research presenting new safer BPA-alternatives. Firstly, a full monomer characterisation (i.e., bio-bisphenols and/or thermoset monomers) including: the phase at RT, colour, purity, viscosity, melting point and crystal structure. Secondly, a preliminary screening of endocrine activity, for example *in vitro* oestrogen receptor transactivation assays using compound concentrations up to the solubility limit, providing quantitative data and allowing statistical comparison between bio-bisphenol structures. Thirdly, a full polymer characterisation including: (i) the molar mass distribution, i.e., $\bar{M}_w$ and $\bar{D}$ -for the thermoplastic polymers- and the degree of cure and cross-link density (e.g., via the rubber elasticity theory) -for the thermosetting polymers-, (ii) general polymer characteristics (e.g., T_g and thermal stability) and (iii) specific polymer characteristics (e.g., crystallinity, solubility, water uptake). Moreover, incorporation of relevant bisphenol reference samples, which show a comparable monomer purity (e.g., wt%, EEW, n), molar mass distribution (i.e., $\bar{M}_w$, $\bar{D}$), degree of cure and/or cross-linking density (e.g., via the rubber elasticity theory), would facilitate the evaluation of the bio-bisphenol's functionality.

To conclude, this review assembled structure–property and structure–toxicity relations from the literature data to assess today's bio-based bisphenol platform and provide more insight for future rational bisphenol design towards safe, renewable and functional BPA alternatives. Hereby, highlighting the importance of a multidisciplinary approach in the

design of new bisphenols providing, in addition to performance evaluation, a preliminary screening of potential hazards, such as for instance the oestrogenic activity.

Author contributions

B. S. and L. T. wrote this article with the aid of S. F. K., I. S., T. H. and P. V. P., reviewing and approving this paper.

Conflicts of interest

There are no conflicts of interest to declare.

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